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THE FRANK E. BUNTS INSTITUTE

announces

A Course In

Diseases of the Gastro-Intestinal Tract

on

MONDAY, TUESDAY, and WEDNESDAY
APRIL 5, 6, and 7, 1937

A complete outline of the course and application blank will be found on pages 76 and 77.

THE CLINICAL AND COMPARATIVE VALUE OF RENAL FUNCTION TESTS

R. H. McDONALD, M.D.

Renal function has to do in general terms with the preservation and maintenance of an optimum environment for body cells. In the unicellular organism where the entire body is in contact with its environment, the process of excretion is a simple matter of diffusion, but in multicellular body masses it becomes necessary that certain specialized cells excrete the waste products of metabolism, excessive water, and salts in order that the chemical composition of the body fluid and cells may remain constant. Specifically, the kidney excretes the waste products of nitrogen metabolism and the excessive inorganic salts, exercising, however, a certain amount of selective action in regard to those salts necessary for the animal economy and excreting others which have no threshold *in toto*. Therefore, these functions are of prime importance in maintaining the viscosity or tonicity of the blood and body fluids and are directly concerned in the maintenance of the hydrogen ion concentration of the body within the narrow limits of fluctuation consistent with health. The kidney undoubtedly acts in accordance with nervous and probably hormonal influences and is profoundly affected by disturbances of endogenous metabolism in other portions of the body. Metabolic disturbances incident to general infections of the body and surgical operations increase the renal load and may be factors which cause insufficiency. Thus some method which will be an index of renal reserve is highly desirable.

It is hardly conceivable that any single ideal test for renal function, especially in the diseased kidney, can ever be attained. It cannot at present be assumed that all the many partial functions of the kidney are equally depressed in a given renal lesion. In fact, there is abundant clinical evidence to show that in one renal lesion the difficulty consists in excretion of the nitrogenous metabolites, whereas in another the difficulty seems to be in regard to the inorganic salts and water. In the past twenty-five years numerous tests have been proposed, each of which has been based on some phase of renal physiologic activity, and many are of definite value if their limited significance is appreciated. It must be recognized that our knowledge of both the pathologic and physiologic processes in the kidney is inadequate. Prognosis must be based on the summing up of a large number of variables of which the functional efficiency of the kidney at any given time is only one. The course of the disease process in nephritis cannot be predicted accurately from a knowledge of the renal efficiency at any one time or even from a knowledge of the rate at which this efficiency is changing over a given period. Furthermore, individual patients differ in the way they withstand a given

degree of renal impairment. The constitutional variables which cause such differences are not within the scope of any renal function test, but can only be gauged in the light of clinical opinion and any other related data. It must be remembered, therefore, that the results obtained from any test are not to be regarded as absolute measures of renal efficiency but rather as relative or comparative values.

Stieglitz and Knight[1] suggest certain criteria by which the value of a renal function test should be judged.

(1) It should be so simple that it requires a minimum of time, both for the patient and the doctor, as well as a minimum of equipment, chemical analysis, etc.

(2) It is a prime consideration that it should cause no harm.

(3) It should, as far as possible, be a specific test of the structures or functions which are to be studied. This admittedly is difficult in view of the inadequacy of our knowledge and difference of opinion as to which portions of the renal unit excrete different substances.

(4) In order to measure accurately the renal ability, the kidney should be placed under stress. It is well known that the total number of functional glomeruli is considerably less in a resting condition than the maximum number which can be called into play. In this respect the renal tissues act in exactly the same way as other tissues.

(5) The test should yield uniform results in normal subjects. No absolute unanimity of results is, of course, to be expected because of the variability of the factors concerned, but it should be possible to establish results within certain limits in normal individuals, deviations from which can safely be regarded as being abnormal.

Despite the difficulties involved in a complex biological problem of this type, a number of tests of renal function have been devised which successfully meet the criteria cited above for the study, prognosis, and treatment of renal lesions. These fall naturally into three general classifications as suggested by Freyberg.[2]

1. Those which test the ability of the kidney to concentrate or dilute the urine.

2. Those which test the ability of the kidney to excrete introduced foreign substances.

3. Those which test the ability of the kidney to excrete normal metabolic wastes.

Concentration and Dilution Tests

It has been recognized for a considerable period that one of the initial evidences of decreasing renal efficiency is to be found in the inability of the kidney to secrete urine of high concentration or conversely of high dilution. The application of this knowledge to the study of

renal function appears to have been made first, by Volhard[3] in 1908. In the test he devised, the renal function is estimated from its ability to excrete urine of large volume and low specific gravity after one and one-half liters of water are drunk and to execrete urine of high specific gravity after a subsequent period in which no fluid is drunk. The test was somewhat modified by Lundsgaard[4] in 1920, and in 1927 Rosenberg[5] added certain precautions to make certain that the body was in a normal and steady state of hydration. For two days before using the concentration or dilution tests which were done on different days, the subject had a controlled diet without unusual variations in salt and with 1500 cc. of water. The weight of the subject was taken during the days before and after the test in order to detect instability of the water balance due to the invalidating factors of extrarenal influences of endocrine, nervous, or metabolic origin.

In this country Mosenthal[6] in 1915 introduced the test which bears his name and which is dependent upon the same general principles. Restriction of diet was found to be unnecessary and the patient is allowed to follow his own desires concerning the intake of foods and fluids. The test depends upon the fact that, with an ordinary fluid intake even at a constant rate per hour, the hourly volume and specific gravity of urine vary markedly during the day in normal subjects and that the extent of the variation diminishes in the presence of nephritis. The urine is collected in 2-hour periods from 8 o'clock in the morning until 8 o'clock at night and in a 12-hour period from 8 at night until 8 the next morning. The specific gravities of the 2-hour specimens and the volume of the 12-hour night specimen are measured. The normal values given by Mosenthal[7] in 1932 are a specific gravity of 1.020 or above in one or more of the 2-hour specimens, a specific gravity difference of not less than 0.009 between the highest and lowest specimens and a volume less than 725 cc. for the 12-hour night urine.

The dilution portion of the test was discarded by Addis and Shevky[8] in their concentration tests in 1922. It had been shown that the dilution test gave less constant findings, was less sensitive, and added no information which was not supplied by the concentration test. The concentration test of Addis and Shevky is performed by having the subject abstain from fluids of all sorts from after breakfast, 8 a. m., until after arising the following morning, 24 hours later. During the last 12 hours of the dry period from 8 at night to 8 in the morning, the urine is collected and the specific gravity of this specimen is measured. No preparatory period or special diet is suggested. Addis and Shevky have found that, in normal individuals who previously have followed an ordinary diet, the average specific gravity of the urine obtained as described above was 1.032, that 95 per cent of tests on normal subjects on ordinary diets showed values of 1.028 or above and 100 per cent were above 1.026.

In making the original concentration tests which Lashmet and Newburgh[9] devised in 1930, the subject remains in bed four days and during the first three a special diet is given consisting of 45 grams of protein, 106 grams of fat, and 180 grams of carbohydrate. The sodium chloride intake is from two to three grams daily and the fluid intake 1500 cc. At 6 p. m. after the patient has had supper on the third day, all intake, both fluid and food, is stopped until noon the following day; all urine is discarded except the specimen obtained from 10 o'clock until noon on the fourth day. The specific gravity of this 2-hour specimen is determined. Lashmet and Newburgh found that all normal subjects concentrated the urine to 1.026 or above on this regimen. In 1932 Lashmet and Newburgh[10] altered their test, omitting the three day preparatory period but the period of desiccation was increased to 24 hours (Table 1).

TABLE 1

LASHMET AND NEWBURGH CONCENTRATION TEST, 1932

All foods and fluids except special dry diet are discontinued for 38-hour period beginning at 10 p. m.

Urine collected from 8 a. m. next morning (second day) to 8 a. m. following morning (third day).

This is specimen 1.

Urine collected from 8 a. m. to 10 a. m. (third day).

This is specimen 2.

Urine collected from 10 a. m. to 12 noon (third day).

This is specimen 3.

Diet is 40 gms. protein Total calories 1900
104 gms. fat 1 gm. sodium chloride added
204 gms. carbohydrate

Total water available, 700 cc. in 24 hours.

Normal subjects concentrate urine to specific gravity 1.029—1.032.

In all these concentration tests, the specific gravity of the specimen must be determined accurately. Any significant amount of protein in the urine will, of course, increase the specific gravity. It has been found that for each per cent of protein in the urine the specific gravity is increased by 0.003. All the concentration tests are based on the ability of the kidneys to excrete urine of high specific gravity and it has been shown that this is a sensitive index of early renal damage. It was pointed out by Koranyi[11] as early as 1899 that the kidney does thermodynamic work in concentrating urea and other solids in the urine to many times their concentration in the blood. The amount of urea contained in 50 liters of blood, for example, is likely to be concentrated into one liter of urine. It takes about as much calculated work to do this as to compress six liters of gas at atmospheric pressure into one liter at six atmospheres. A damaged kidney cannot accomplish this concentration.

Excretion of Introduced Substances

The chief representative of the second group cited above is the phenolsulphonphthalein test which was introduced by Rowntree and Geraghty[12] in 1911. It was pointed out by Rowntree that the evidence of decreasing renal function was a flattening of the excretory curve and it has been demonstrated by several workers that the total 2-hour excretion is a poor index of renal ability since even a damaged kidney may excrete from 50 to 60 per cent of the dye in the 2-hour period. However, the use of the fractional phenolsulphonphthalein test has, to a large extent, improved the efficiency of the test. The technique is shown in Table 2.

Table 2

Fractional Phenolsulphonphthalein Test

Patient drinks 600 cc. water and empties bladder 30 minutes before test is commenced.

6 mg. (1 cc.) of sodium salt of phenolsulphonphthalein is injected intravenously.

Specimens of urine collected at 15 minutes, 30 minutes, 45 minutes, 60 minutes, and 120 minutes.

Estimation of dye content with Duboscq colorimeter using freshly prepared standards with phenolsulphonphthalein.

Normals, (Chapman and Halsted[13])

2 hour totals varied from 63—84 per cent
15 minute excretion 28—52 per cent
30 minute excretion 12—24 per cent

Excretion of Normal Metabolic Wastes

The third group of renal function tests are those which are based on the excretion by the kidney of normal metabolic waste. It has been shown repeatedly that the absolute level of the urea, uric acid, creatinine, and other nitrogenous metabolites, or of the inorganic salts of the blood is of no value in determining the extent of renal damage, since increased concentration of these substances in the blood does not occur until approximately five-sixths of the renal units have been rendered functionless. Thus normal blood urea is a common finding during the greater part of the course of any renal lesion, even in the face of overwhelming clinical evidence and urinary signs of severe renal damage. In the acute phase of hemorrhagic Bright's disease, uremia may be noted due to the temporary disturbance of a large proportion of the kidney. With recovery from the acute phase, these excessive nitrogenous wastes are reduced to a normal level and continue at this level unless further acute phases occur. This continues until progressive degeneration reduces the number of renal units to a number below that absolutely necessary for excretory function, and the stage of renal insufficiency or terminal Bright's disease is reached. This may cover a period of many years. Further-

more, increased nitrogenous metabolites of the blood may be distinctly increased in conditions entirely apart from renal disease and in the presence of normal kidneys. In severe dehydration, the level of the blood urea may be considerably increased, due to a concentration of the blood. In obstructions of the upper intestinal tract, the level of the nonprotein nitrogen of the blood may be increased rapidly to uremic levels. In this instance, beside the factor of dehydration, there is also in all probability a factor of increased production of nonprotein metabolites due to an increased endogenous catabolism, perhaps related to the production of toxins from the gastro-intestinal tract. In both these cases, the condition subsides quickly provided the etiological factors can be corrected. In severe grades of urinary obstruction it is also very common to see high blood urea readings without uremic manifestations, but this subsides within a few days when the obstruction is relieved. These blood chemistry readings are, therefore, of little value in themselves as far as the degree of renal function is concerned, although they are indicative of severe renal damage if nonrenal sources can be eliminated.

However, it has been possible by a simultaneous study of the concentration of nitrogenous metabolites in the blood and in the urine to develop tests which have been exceedingly important and useful in determining renal function. It has been found that the excretion in the urine of several substances of widely different chemical nature have one property in common; that is, for each of them the rate of excretion in the urine is, under proper conditions, directly proportional to the concentration of the blood. From this it follows that the ratio of excretion rate to blood concentration is a figure independent of the actual concentration in the blood over a wide range. It is this figure which is believed to indicate the excretory efficiency of the kidney toward the subject under consideration. By clearance, therefore, is meant the rate of excretion of a substance, expressed in milligrams per unit of time divided by the average concentration of the substance in the blood plasma during that time, expressed as milligrams per cubic centimeter. The clearance figure represents that volume of blood which would contain an amount of the substance under consideration equal to the quantity excreted in unit time in the kidneys. It is assumed, merely for convenience, that the blood flowing through the kidney is completely freed or cleared of this substance before leaving by the renal vein, although actually, it has been shown that only a small percentage (10.5 per cent—Van Slyke) of the blood content of the substance is actually eliminated during its renal circulation.

The most important of these clearance tests is the urea clearance of Van Slyke[14] although the same principles may be applied in regard to uric acid and creatinine and also to the inorganic salts. The technical

difficulties of estimating these latter substances have made the use of urea by far the most common test substance.

Historically the conception of the urea clearance test goes back to observations made by Bright in 1826 when he noted markedly increased plasma nonprotein nitrogen concentration with reduced urinary concentration in patients with severe renal disease. The conception of the simultaneous studies of the blood and the urinary concentrations of these excretory products has been advanced by many investigators during the intervening period, particularly by Ambard in France and by Addis and Van Slyke in this country. Addis[8] believed the urea excretion ratio to be independent of the volume of the urine, and he recommended its determination, that is, the urea in a one-hour specimen of urine over the urea in 100 cc. of blood, as an index of renal function. Van Slyke has shown that this ratio is valuable where the urinary flow is 2 cc. or more per minute but that with a lower flow of urine, the excretion rates vary more nearly in proportion to the square root of the urinary volume. The idea that the urinary urea excretion is directly proportional to the blood urea content when the urinary output is above 2 cc. per minute has been confirmed by several observers. Below this level which has been fixed as the augmentation limit, the urea excretion rate falls, not in direct proportion to the decrease in volume but, on the average, in proportion to the square root of the volume. Thus two formulas are necessary, one for urinary volume over 2 cc. per minute, the so-called maximum clearance, and the other for lesser urinary volume, the standard clearance. The technic of this test is outlined in Table 3.

Invalidating Factors

A number of factors may invalidate the results of concentration tests. It has been shown by Addis and Shevky[8] that extrarenal influences of endocrine, nervous, or metabolic origin could increase the water output or decrease the solid output during the period of test and thus produce a lowering of specific gravity simulating that caused by renal deficiency. An unusually low nitrogen or salt content of the diet might similarly influence the results. Unusual desiccation or conversely water flooding of the subject during the days preceding the test, storage or excretion of edema fluid in subjects of the nephrotic type during the test, and cardiac decompensation might seriously disturb the results without necessarily indicating renal damage. Mosenthal[15] states that a low fixed specific gravity may be found in many widely varying conditions—marked anemia, elimination of edema, pyelitis, polycystic kidney, prostatic hypertrophy, urethral stricture, cord bladder, and diabetes insipidus. Despite the possible interference of such invalidating factors, however, it has been a matter of experience that when signs

of renal lesions exist or have existed, consistently low results in concentration tests afford presumptive evidence that renal damage exists—in some cases, even in the presence of normal urea clearance tests.

TABLE 3

Bladder emptied. Catheterization if there is doubt regarding complete emptying of bladder.

Specimen of urine collected at end of first hour.

Specimen of blood collected at end of first hour.

Specimen of urine collected at end of second hour.

Specimens of blood and urine analyzed for urea content.

Maximum clearance

$$Cm = \frac{U \times V}{B}$$

Standard clearance

$$Cs = \frac{U}{B} \times \sqrt{V}$$

U = Urinary urea in mg. per 100 cc.

B = Blood urea in mg. per 100 cc.

V = Urinary volume in cc. per minute.

Final result expressed in percentages of normal on basis of average of 75 cc. per minute for maximum and 54 cc. per minute for standard.

Normal result, 80 — 120 per cent.

In regard to the blood urea clearance test, the most important single factor which may tend to falsify results is a failure to obtain all the urine formed by the kidneys during the period of the test. Prostatic obstruction, diverticula of the bladder, cystocele, and incontinence usually account for these failures which may be prevented largely by the use of the catheter. Where there is a constant amount of residual urine in the bladder, the clearance test is only slightly falsified because the urea excretion is compared with the concentration of the urea in the blood which varies but little during short periods of time.

The formulas used in calculating urea clearance contain a factor that corrects for variations in urea excretion at different rates of formation of urine. However, when the urinary flow is very small, the urea clearance calculated as usual fails to indicate correctly the renal efficiency. Thus it has been shown that with a urinary volume of 20 cc. or less, the urea clearance test gives a decidedly low reading whereas in the same individual with adequate urinary output, normal values may be obtained. This difficulty may be obviated readily by administering a sufficient amount of fluid before the test begins.

In the phenosulphonphthalein test, the most obvious cause of error in results is to be found in the numerous opportunities for error in technic. These include the question of exact quantitative injection, accurate timing, and failure to collect all the urine excreted in the given period. Residual urine in this case will result in an error of much greater magnitude than in the urea clearance test because the quantitative recovery of a substance not normally present in the blood and urine is required. Catheterization again will lessen this source of error. In the measurement of renal function during pregnancy, the phenolsulphonphthalein test usually is found to give a decidedly low reading. This has been explained on the basis of several factors: (1) the additional fetal circulation; (2) an altered blood flow through the kidneys due to the tumor of pregnancy, and (3) the hydronephrosis known to exist commonly during pregnancy. In cases of severe hepatic damage, the excretion of the dye through the biliary tract is diminished and that portion of the dye which is excreted in this fashion is thus held in the blood stream. The result is that a higher percentage of the dye is excreted by the kidney and consequently a higher functional result is secured for the phenolsulphonphthalein test than normally would be the case.

With regard to the application of these tests to urological problems, it is at once apparent that another element is added here—the element of urinary obstruction which may accompany parenchymatous renal disease or if prolonged may produce it. If the factor of urinary obstruction can be removed, the renal function tests are at once applicable for the appraisal of the renal efficiency. It is frequently seen that a low clearance value, for instance in an individual with prostatic hypertrophy, is increased considerably by vesical drainage, although the values are usually still well below normal, due perhaps to both pressure over a period of time as well as to the possibilities of renal damage of other origin. In pure urinary obstruction, many of the usual signs of renal insufficiency of parenchymatous origin are missing, for example, hypertension. There are no retinal changes, there is little difficulty with excretion of water, and edema is rarely encountered. Blood urea values of over 200 mg. per 100 cubic centimeters are common without uremic manifestations and subside quickly on relief of obstruction. Estimation of the function of the two kidneys separately may frequently be necessary in unilateral renal lesions. Concentration and clearance tests are not readily applicable and since quantitative ureteral collection of urine is inaccurate, the divided phenolsulphonphthalein is open to question although still used. Urea concentration of individual specimens may be an index of function. The appearance, time, and intensity of color from injected indigocarmine is widely employed either by use of ureteral catheters or by visual inspection through the cystoscope.

More recently, the use of serial roentgenograms in intravenous urography at five minutes, fifteen minutes, and one-half hour have been used as an index of separate renal function.

In summary, therefore, it appears that the concentration tests done after an adequate preliminary regimen and with correction when necessary for the effect of protein on the specific gravity constitute the most sensitive tests for qualitative detection of damaged renal function. It has been shown that this finding may occur before any reduction is noted by the urea clearance or phenolsulphonphthalein test in patients who have obvious renal damage, as evidenced by urinary signs. Such a condition exists in mild acute nephritis, in nephrosis, and very frequently in the early stages of arteriosclerotic Bright's disease. The concentration test possesses the great virtue of simplicity without quantitative collection of urine and without the necessity for any quantitative chemical analyses. It also most satisfactorily meets the requirement of putting the organ in question under functional strain. It has been suggested that this test measures fairly accurately the tubular ability inasmuch as theoretically at least the tubules are concerned with the absorption of water from the glomerular filtrate, thus concentrating the urine. This point cannot, at the present stage of our knowledge, be accepted as absolutely proved. It may be pointed out that when a concentration test yields urine of more than 1.026 specific gravity, one may assume as a general rule that the renal function is normal and other tests are unnecessary. When the patient is recovering from acute nephritis, persistent low gravities may continue to show some evidence of residual renal abnormality for weeks or months after the urea clearance test has returned to normal. As an aid in determining when recovery is complete, therefore, the concentration test is significant.

For measuring the degree of renal damage, however, concentration tests do not appear to be entirely suitable. Although the extent of fall in urine concentration shows some statistical correlation to the urea clearance and to the severity of renal disease, the disagreement in given cases may be extreme. A patient who has practically recovered from an acute nephritis and regained a normal urea clearance may, by concentration tests, continue to yield urine of low specific gravity for some time just the same as a patient in terminal uremia with a very small proportion of normal clearance. In cases of chronic nephritis sufficiently advanced to show urea clearances of 20 to 30 per cent of normal, concentration tests may already show minimal specific gravity of the urine and then will reveal no further changes during the subsequent progress of the disease while the clearance continues to fall until it reaches the uremic level of 3 to 5 per cent. The urea clearance test appears to mirror more accurately the progress of the renal lesion and offers the best method at present for following the patient's progress. It

is unfortunately more cumbersome and requires the chemical analysis of the blood as well as the urine. It is thus not generally suitable for use in the private office but ought to be available in any hospital where surgery is performed. Against it also has been brought the argument that it does not place the kidney under conditions of stress.

The two-hour phenolsulphonphthalein excretion test is not a sensitive test for renal efficiency. The fractional method as advocated by Young[16] has certainly increased the accuracy of the test, and the 15-minute dye excretion appears to be a sensitive index of renal function. The technical difficulties render it somewhat less reliable. It would appear safe to conclude that when the 15-minute specimen contains 28 per cent or more of the injected dye, the renal function is adequate. With low excretion of the dye, interpretation is somewhat hazardous.

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THE CORRECTION OF SCOLIOSIS BY USE OF A MODIFIED TURNBUCKLE JACKET

J. I. KENDRICK, M.D.

The treatment of scoliosis in all its degrees has presented to the orthopaedic surgeon one of his most difficult problems. Treatment in the early and milder cases of lateral deviation of the spine has been more successful than in the severe cases with marked deviation and fixed deformity where less satisfactory results have been obtained. The more severe and the more fixed the deformity, the more drastic must be the treatment. The problem presented by the correction of these more severe cases has interested me and a modification of the turnbuckle jacket has been devised in an effort to secure more satisfactory results.

Much has been accomplished during the last forty years in the treatment of the patient with severe scoliosis and an impetus for the development of more satisfactory methods has come from the better understanding of the pathogenesis of scoliosis as well as the realization that a very good degree of correction can be obtained. Bradford and Brackett[1], Lovett and Brewster[2], Abbott[3], Forbes[4], and Galeazzi[5] were the earlier workers whose methods of correction gave such encouraging results that other applications of their principles have been developed and still better results are being obtained.

The curving spine has been shown invariably to undergo a change due to torsion and this is spoken of as rotation. It is this torsion change which accounts for so much of the deformity. As the rotation occurs, the ribs are carried backward on the convex side of the curve and forward on the concave side of the curve with resulting asymmetry and deformity. The recognition of this rotation and the application of a derotating force has aided greatly in the correction of severe curves.

Traction on the spine was one of the earliest forces applied for correction. In the fixed curved spine, a traction force sufficient to move the curve was unbearable to the patient, but it has always been recognized that such a force, though moderate, is of value. This force stretches the contracted muscles and ligaments and distracts the articulations and when constant, even though moderate, has a definitely corrective effect. Using the ends of the curve as fixed points and the apex as a fulcrum, a more powerful force can be applied and a force which the patient tolerates well. This force has been utilized in many of the corrective methods but has not been applied as constantly and as accurately as in the case of the turnbuckle jackets described by Risser[6] and Brewster[7].

Various workers have used the turnbuckle principle with very good results but no consideration has been given to the increased

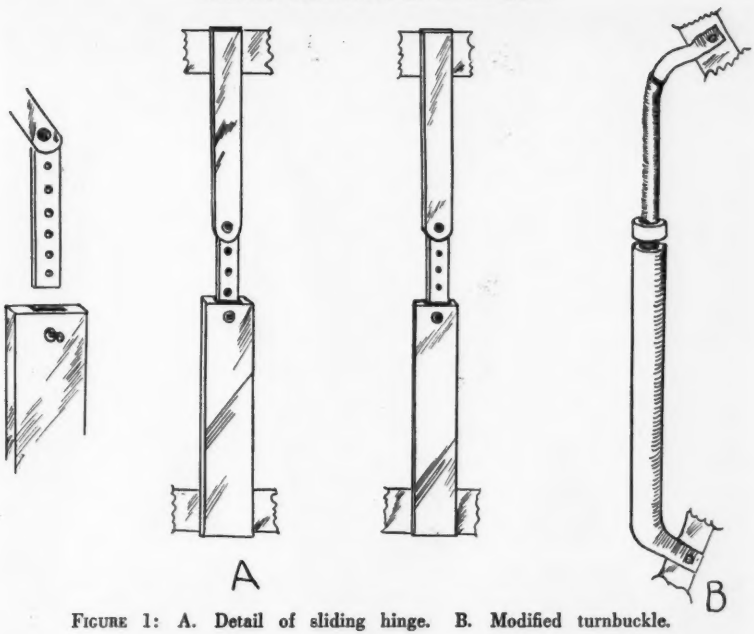

FIGURE 1: A. Detail of sliding hinge. B. Modified turnbuckle.

length of the spine as the curve is straightened. In using a fixed hinge in the jacket, there is a jamming effect upon the bodies and the articulations as this increase in length develops and progress in correction becomes slow or ceases. Garceau[8] pointed out the advantage of the addition of a traction force to the hinge so that, as the spine increases in length as the turnbuckling progresses, the jacket accommodates for it. Following this suggestion, a hinge was designed (Fig. 1) with a sliding collar in order that a degree of distraction can occur as the turnbuckle is advanced. By this means, a degree of traction on the spine is maintained and the jacket is lengthened to accommodate it to the lengthening spine.

The general principles of the jacket (Figs. 2 and 3) are in accordance with those of the Risser jacket but, with the addition of the traction hinge, a few modifications have been found necessary. The jacket may be thought of as comprising two segments—the one controlling the upper end of the curve and the other the lower end. The more accurate the control on these segments, the more effective will be the corrective force applied. To gain this control, the plaster is extended down over the arms for a short distance and it is applied to both thighs with the legs in considerable abduction. With the jacket applied in this fashion, the traction gained as the hinge distracts is transmitted to the spine and is not

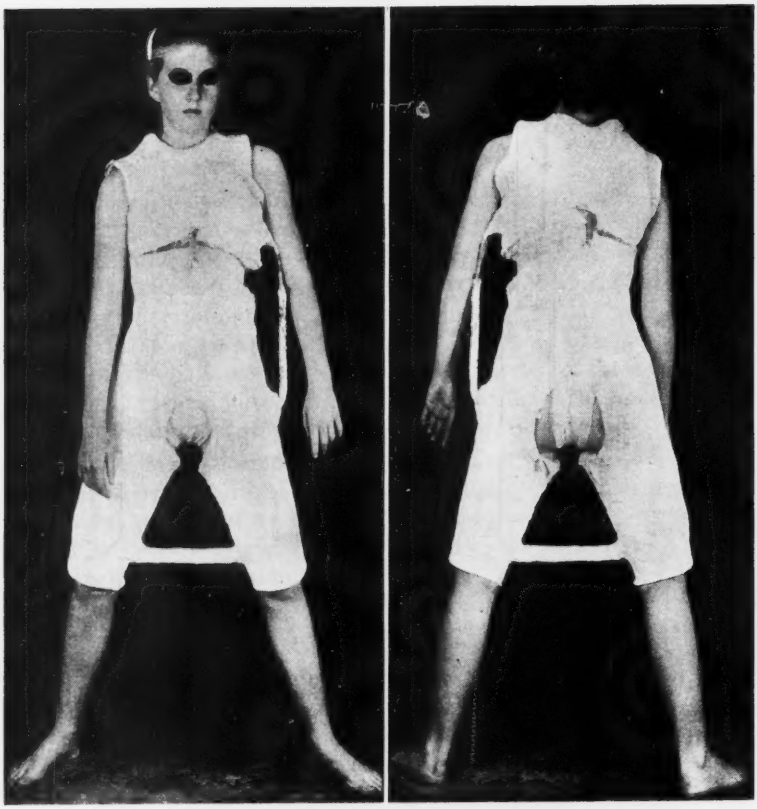

FIGURE 2: The modified turnbuckle jacket.

lost by the plaster merely sliding down the leg. In the low dorsal and in the lumbar curves, the arm cuffs have not been necessary. In the high dorsal curves it has been found necessary to incorporate a collar.

The jacket is applied in one piece with the patient standing and with a moderate degree of head traction. This traction improves the contour of the body and accomplishes that degree of correction which can be gained easily. Great care must be taken to pad the points of pressure thoroughly. The jacket should be made quite sturdy as the period of correction may extend over 6 or 8 weeks. After the first layers of plaster have set, the hinges and turnbuckle are incorporated, using sufficient plaster to anchor them securely because they often loosen due to frequent turning of the patient, and they can never be reapplied as securely as at first. When the

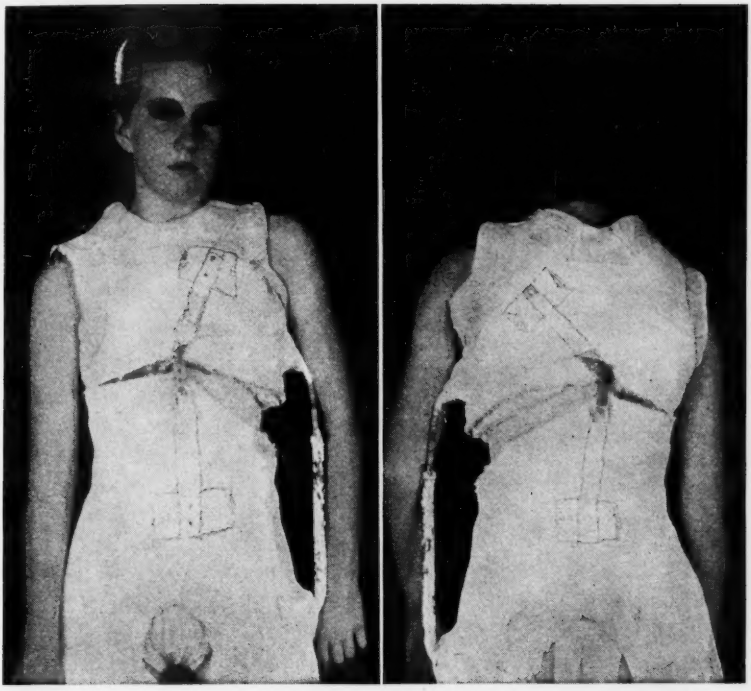

FIGURE 3: The jacket showing detail of the incorporated hinge.

jacket is thoroughly dry, it is cut horizontally at the level of the hinge. This horizontal cut also represents the apex of the curve to be corrected. A keyhole saw makes this cutting easy. The screws are then removed from the sliding collar of the hinge and distraction is effected by advancing the turnbuckle. When a two inch interval has been gained between the segments of the jacket, the screws are reapplied and the collar is locked so that the force of the advancing turnbuckle is transmitted to the hinge, and lateral flexion results. The collar is intermittently locked and unlocked until a considerable degree of correction and lateral flexion has been gained. When this considerable degree of lateral flexion has been approached, it may be necessary to cut away sections of the plaster on the side opposite the turnbuckle so that further lateral flexion can be obtained. Areas of pressure must be watched for and, if discovered early, they can be aborted by releasing the corrective force.

I shall not discuss the maintenance of correction but, in these severe cases, the structural changes in the soft tissues and in the

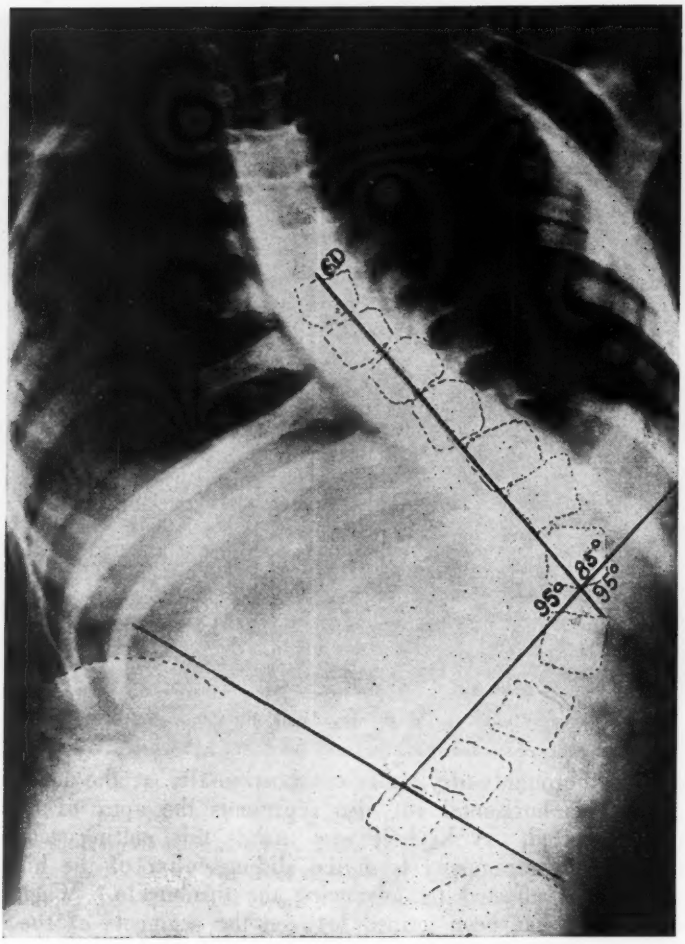

FIGURE 4: Roentgenogram before correction.

bones necessitate quite a rigid and accurately applied support. Long spinal grafts have been found to hold the correction well and in several of these cases fusion has been done through a window cut in the corrective jacket.

The patient whose roentgenograms are shown in figures 4 and 5 was an eleven year old boy whose scoliosis had developed slowly over a period of 7 years after an attack of poliomyelitis. The spine was fairly flexible and this flexibility was further increased by a period of mobilizing exercises. The weight-bearing picture (Fig. 4)

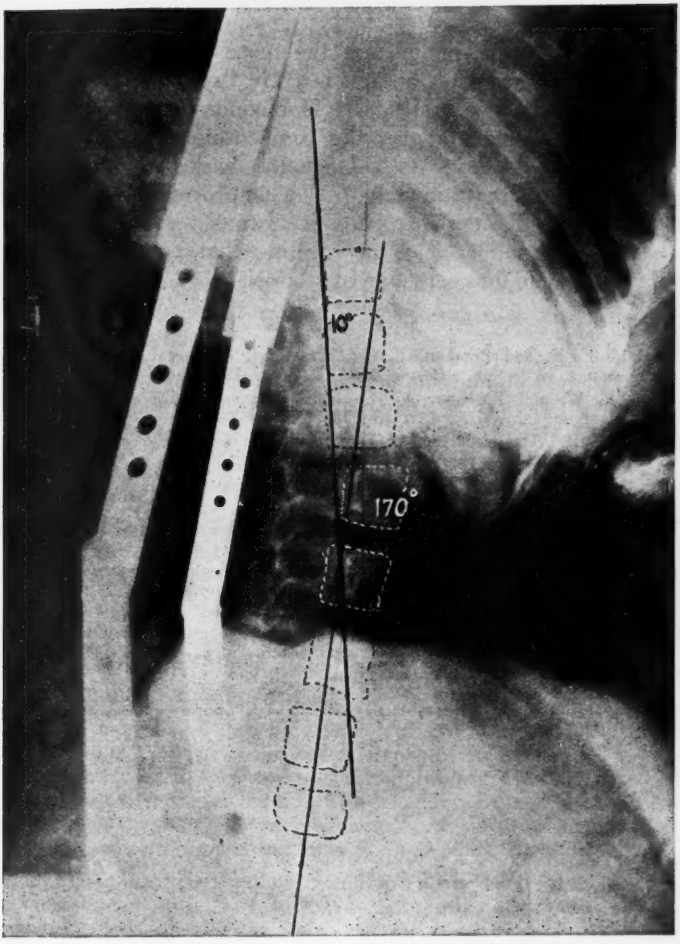

FIGURE 5: Roentgenogram after correction.

shows a dorsolumbar curve of almost 90 degrees with marked pelvic obliquity and the chest margin approximating the iliac crest. The roentgenogram (Fig. 5) showing the correction in the turnbuckle jacket was taken 8 weeks after the jacket had been applied. In this picture it can be seen that the pelvic obliquity has been corrected and the dorsolumbar curve reduced to 10 or 15 degrees.

Time and diligence are essential in correcting severe scoliosis. I have been surprised at the degree of correction that can be obtained, and if the corrective forces are applied slowly, rarely do the patients

complain. It is my belief that the more nearly straight one can make these curved spines before they are fixed, the more serviceable the back will be eventually. It is obvious that if the deforming curve is quite an acute one, the compensatory curves are proportionately acute in order to balance the back, and strain and discomfort will occur ultimately. The improvement in the appearance of the back after correction is always very gratifying. From these two standpoints, it is my feeling that considerable attention should be given to the correction of scoliosis.

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Photographs of jacket and roentgenograms used through courtesy of the Texas Scottish Rite Hospital for Crippled Children, Dallas, Texas.

URETERAL TRANSPLANTATION IN THE VERY YOUNG

Report of a Case

WILLIAM E. LOWER, M.D.

The most frequent indication for transplantation of the ureters into the rectosigmoid in young children is exstrophy of the urinary bladder. Time will not correct the condition nor will the deformity improve with years. Unlike some other deformities, no compensatory function is to be expected; on the contrary, the situation becomes worse for both the child and parents as the child grows older. In addition, the danger of damage to the kidneys increases with years.

At what age, then, can a successful transplantation be accomplished? Formerly we were of the opinion that one should wait until the child had been taught voluntary control of the anal sphincter or from three to five years of age. If the anal sphincter is functioning, we now believe the earlier the ureters are transplanted the less will be the danger of complications, such as ascending infection of the urinary tract. We know that very young children tolerate surgical procedures remarkably well as is attested by operations for cleft palate, harelip, pyloric stenosis, intussusception, etc. As an example of the tolerance and result of early operation for exstrophy, the following case is presented in which operation for exstrophy of the bladder was performed on a patient four and one-half months of age.

This patient, a baby boy 4 months of age, was first seen in the Clinic on June 22, 1936, with marked epispadias and exstrophy of the bladder. The baby was a full term child and the delivery was uncomplicated. He was breast fed, had developed normally, and at the time of admission, his general health was excellent and no other abnormalities were noted. Examination of the blood showed 4,540,000 red cells, 71 per cent hemoglobin, and 13,650 white cells.

Transplantation of the ureters into the rectum was advised and for this purpose the patient entered the hospital on July 2, 1936. On the day of admission he was given cleansing enemas of saline solution until the return was clear. Another enema was given four hours before operation. Feedings were withheld for twelve hours before operation. On the morning of July 3, 1936, the left ureter was transplanted under general anesthesia into the sigmoid. The operation was carried out through a lower left rectus incision and the ureter was transplanted, using the Coffey I technic. The patient was given nothing by mouth except very small amounts of sterile water for the first 12 to 16 hours after operation. Following this the usual nursing regime was started. A rectal tube was kept in place for the first five postoperative days for continuous drainage. This was irrigated frequently with small amounts of saline solution. For the first two or three days postoperatively, the patient had a rather poor appetite and was somewhat irritable, but after this his disposition improved and he appeared to be a normal, happy baby. He had a slight rise in temperature following operation, but this promptly fell to normal by the second day and remained so. The wound healed by primary intention.

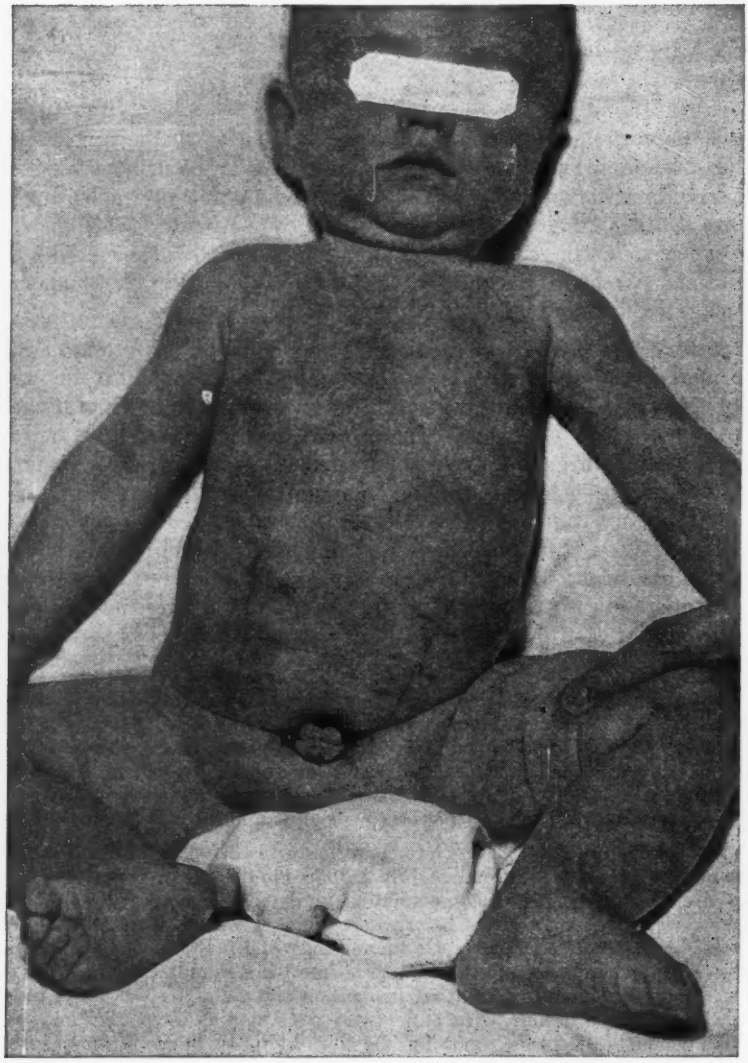

FIGURE 1: Photograph of patient nine days after second operation.

The right ureter was transplanted into the sigmoid on July 14, 1936—the eleventh postoperative day—by the previously used technic. The pre- and postoperative care was the same as that at the first operation. Following the second operation there was a rise in temperature to 103.5°F. with a return to normal by the second postoperative day where it remained during the balance of the hospital stay. The patient had a somewhat greater immediate reaction

from the second operation, but by the fourth postoperative day his disposition and appetite had returned to normal. The second incision likewise healed by primary intention, and the patient was discharged from the hospital on his twenty-first hospital day which was nine days after the second operation (Fig. 1).

The baby was last seen on October 27, 1936. He had gained four pounds in weight and appeared quite healthy. He apparently had good control of the sphincter and was able to hold his urine for a period of four or five hours.

This child is the youngest on whom we have performed transplantation of the ureters for exstrophy of the bladder, and the postoperative results in this case, compared with those in older children, lead us to believe that this is a much more favorable age for operation.

PROTAMINE-ZINC-INSULIN IN DIABETES

E. PERRY MCCULLAGH, M. D.

Since the appearance of Hagedorn's paper in January, 1936,[1] regarding the use of protamine-insulin, a wide interest in it has developed. The original claims that it had a prolonged action, gave better control in most cases, a tendency to less frequent insulin reactions with a diminishing number of injections and a reduction in actual dosage have largely been corroborated by other investigators.[2,3,4,5] More recently, the addition of zinc to protamine-insulin has received considerable attention and it appears likely that a combination of the zinc with protamine will supercede the use of plain protamine-insulin.

The observations reported in this paper were gathered in the management of forty-eight patients, some of whom had been treated with various preparations of protamine-insulin since February, 1936. Since August of 1936, all patients in this group have received protamine-zinc-insulin. Cases of all degrees of severity have been treated and four children are included in the group. The ages of the patients vary from 8 to 76 years.

It has been felt advisable to hospitalize all patients during the first part of their treatment. The hospital stay averaged fourteen days. No patient was confined to bed except for some complication. An attempt was made in each case to maintain physical activity comparable to that of the patient's average day. During the hospital stay, venous blood was taken routinely for determination of the blood sugar at 8 a. m., 12 noon, 4 p. m., and 10 p. m. daily and in some cases at other hours in addition, the Myers-Bailey[6] method being used. Twenty-four-hour specimens of urine were collected in four periods daily, the periods ending before meals and at bedtime. Each specimen was tested for sugar by Benedict's qualitative method and when sugar was present, the 24-hour excretion was calculated in grams, Benedict's quantitative method being used. Qualitative estimation of ketone bodies was done on all urine containing more than 1 per cent glucose.

PREPARATION

The protamine-zinc-insulin used in this investigation contained 40 units of insulin per cubic centimeter and approximately 0.08 mg. of zinc in combination with protamine in a buffered solution. Since the active material is present in fine particles, careful, gentle mixing is important before the withdrawal of each dose. The use of a cool, dry syringe is advised and it is recommended that subcutaneous injection be done in such a way as to insure a depot of precipitated insulin in the subcutaneous tissues. Originally it was thought necessary to mix the insulin with the protamine buffered solution a few days prior to its

use but since it has been established that the mixture is stable for at least six months, the material is now supplied ready mixed in 5 cc. vials, each vial bearing the date after which its stability cannot be guaranteed.*

The Diet

We have been accustomed to use a high carbohydrate, relatively low fat diet for some years and this practice has been maintained. In our attempt to control diabetes of various degrees of severity with one dose of protamine-zinc-insulin, we have in some cases tended to be less rigid regarding the low level of fat which is usually maintained in such diets. The number of grams of fat per day in the routine diet was 60. It is our impression that a smooth control is more readily obtained when the carbohydrate content of the diet is not elevated above 200 grams per day. Some patients have received 250 grams of carbohydrate per day and the carbohydrate intake has been 175 grams per day or more in 32 of the cases. The average daily intake in the entire group has been: carbohydrate, 181 grams; protein, 66 grams; and fat, 76 grams.

The diet for each individual is calculated on the basis of the basal caloric requirement for ideal weight. In obese individuals, we have not usually found it advisable to use a daily caloric intake below such a figure as this is usually considerably less than the basal caloric requirement for actual weight and thus produces a daily caloric deficit sufficient to maintain loss in weight where this is required. In most instances, the total caloric intake ranges between the basal caloric requirement and 40 per cent above it.

The diet has been divided routinely into three meals containing 30 per cent, 35 per cent, and 35 per cent respectively of available glucose. Considerable manipulation of this distribution is advantageous at times. With the use of protamine-zinc-insulin, it has not been found to be of frequent advantage to use one meal containing only 20 per cent of the daily available glucose as it was found by Hagedorn, et al,[1] and Root, Marble, et al,[2] using plain protamine-insulin. In some cases we have divided the daily intake into four meals, giving a small proportion of the food as a luncheon at bedtime. This has the advantage of creating an evener intake of food throughout the 24 hours and thus offsets to some degree the tendency to fasting hypoglycemia. In those cases in which there is an undue rise of blood sugar by noon, it is an advantage to deduct the food for the bedtime lunch from the regular breakfast.

Duration of Activity of Protamine-Zinc-Insulin

Estimates of the duration of activity of a single dose of protamine-zinc-insulin in the human have been obtained from three types of observations.

*The protamine-zinc-insulin used has been generously supplied through the courtesy of Dr. F. B. Peck and the Eli Lilly Company.

1. The effect on the blood sugar level of a single dose given with one meal after which the patient is required to fast until such time as the blood sugar level tends to rise again after the action of the insulin is diminished.

2. The number of hours during which blood sugar levels can be controlled by a single dose when the patient is receiving regular meals. This type of observation applies obviously to those cases in which the diabetes is of such a degree of severity that the blood sugars are almost but not completely controlled by diet alone.

3. The third type of clinical observation which indicates definitely that the insulin compound acts for more than a day is the commonly

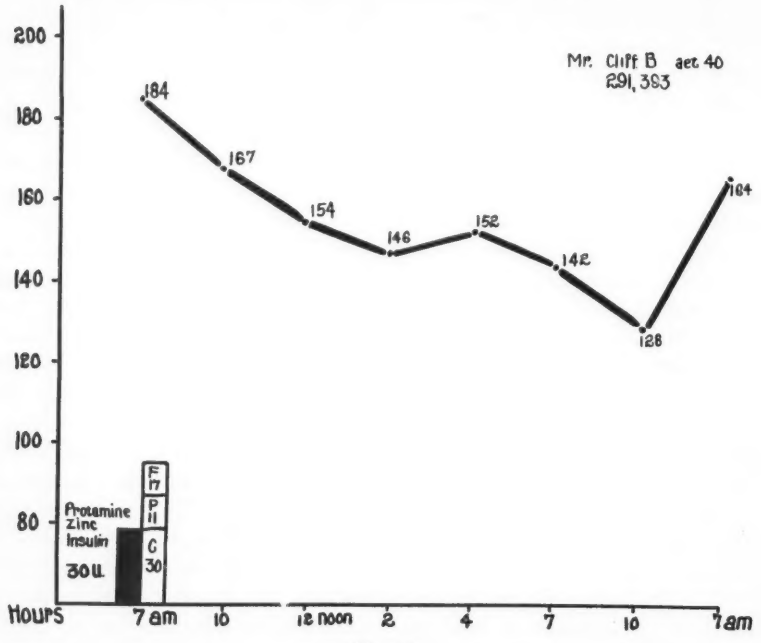

Chart 1

observed cumulative effect of daily doses over the first three days of its administration.

Chart 1 shows the effect of a single dose of protamine-zinc-insulin given at 7 a. m., at which time a breakfast of 30 grams of carbohydrate, 11 grams of protein, and 17 grams of fat was given after which the patient had no more food for 24 hours. The distinct fall in blood sugar levels is obvious within three hours, and from then on the fall is gradual and consistent and is still falling at 15 hours. In 24 hours, however, the

action has distinctly diminished. In several observations of this type, the maximum effect appears in about 18 hours. Larger doses, however, may maintain hypoglycemia for a much longer time, as in Rabinowitch's[5] case in which a single dose of 50 units of protamine-zinc-insulin maintained hypoglycemia for more than 36 hours.

The second type of observation mentioned is visualized in chart 2. In this patient the diet containing C. 100, P. 50, and F. 60, controlled blood sugar levels through the day except the fasting levels which were 150 to 160 mg. per hundred cubic centimeters. A single dose of protamine-zinc-insulin was given as can be seen by the chart, on the morning of October 28. It will be noted that the fasting blood sugar levels were normal for two subsequent days, after which they rose to their original levels. Another single dose of protamine-zinc-insulin at that time controlled the fasting blood sugar levels for two subsequent days.

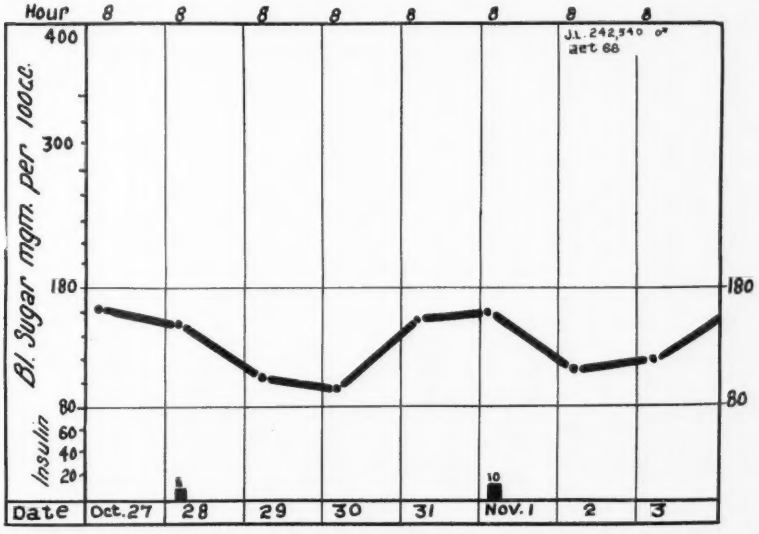

Chart 2

The cumulative effect of daily doses of protamine-zinc-insulin is observed in nearly every instance in which the use of this material is begun. The maximum cumulative effect usually appears to be most marked on the third day and is most obvious in comparing the fasting blood sugar levels. This appears to indicate that the dose given on the first of three days is still active to some degree on the third and also shows clearly why a reduction in dosage, as compared to regular requirements of insulin, usually is necessary. Subsequent reduction in dosage is necessary in many instances. A part of this reduction in dosage is

presumably due to improved control but often makes it difficult to demarcate clearly where the cumulative effect actually is maximal.

Chart 3 shows the blood sugar levels in a case in which fairly satisfactory control was obtained with three doses per day of regular insulin, the doses being given at 8 a. m., 5 p. m., and 10 p. m. The first day depicted on the chart is a fairly typical representation of the previous control obtained and it will be seen that the total required daily dose of regular insulin was 67 units. The patient had a mild afebrile infection of one great toe and had been under control with regular insulin for two weeks prior to the use of protamine-zinc-insulin. On the morning of November 3, 60 units of protamine-zinc-insulin were given in a single dose and this dose was repeated the following day. As will be seen, the fasting blood sugar level on the third day was distinctly lower than

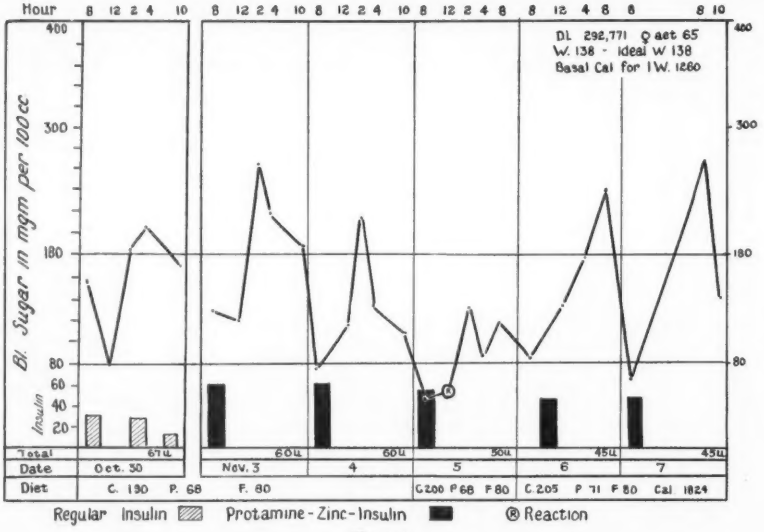

Chart 3

were those the first two days and on this day it was necessary to make an addition to the diet because of excessively low blood sugar levels. When the dose of protamine-zinc-insulin was reduced sufficiently to allow fasting levels to rise to the normal range, normal blood sugar levels during the day were not maintained, indicating the necessity for an additional small dose of regular insulin. This patient was subsequently well controlled with a morning dose of protamine-zinc-insulin of 36 units, together with a dose of 6 units of regular insulin at noon. The total dosage of insulin required to obtain excellent control was, therefore, 42 units, whereas control which was not entirely satisfactory on regular insulin alone had required 67 units per day. The infection

had shown no apparent variation of consequence during the period of time mentioned.

Number of Injections

Since the duration of activity of each dose of protamine-zinc-insulin is distinctly longer than 24 hours, there seems to be little or no advantage in giving more than one dose of protamine-zinc-insulin per day. A single dose per day usually is sufficient to control fasting blood sugar levels and the degree of depression of these levels apparently marks the limit of increase of the protamine-zinc-insulin dose.

Time of Injection

Although the duration of effect of a single dose is longer than 24 hours, its effect is diminished in most instances after 18 hours. This being true, it seems advisable in most cases to give the single daily

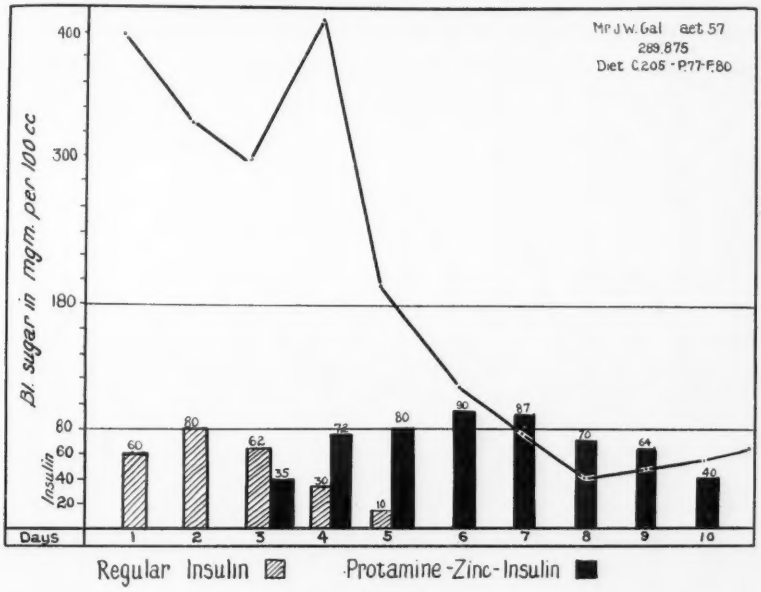

Chart 4

dose at a period longer than 18 hours prior to the low level of the day. For this reason, we have recently used the single daily dose before breakfast in each instance.

Estimation of the Dose

In estimating the dose of protamine-zinc-insulin two chief factors must be borne in mind—firstly, that the effect is cumulative as shown above, and secondly, for this reason the total daily dose requirement must

invariably be less than the regular insulin requirement. Due to improvement in control, the required dosage may subsequently fall considerably. Where poor control is present and rapid improvement can be anticipated, this cumulative effect may be dangerous if it is not considered carefully.

Chart 4 shows the fasting blood sugar levels in a case in which control was poor while the patient was receiving 60 units of regular insulin per day. On raising the daily dose of regular insulin to 80 units, the blood sugar levels fell somewhat but were still far above the normal range. Instead of first obtaining good control with regular insulin as we subsequently have found advisable, it was decided in this case to change to protamine-zinc-insulin, arranging a combination of protamine-zinc and regular insulin in such a way as to make the dose approximate 90 to 95 units per day. After the use of protamine-zinc-insulin for three days, the fasting blood sugar levels had fallen to the normal range. The dose was not reduced sufficiently at this time and the hypo-

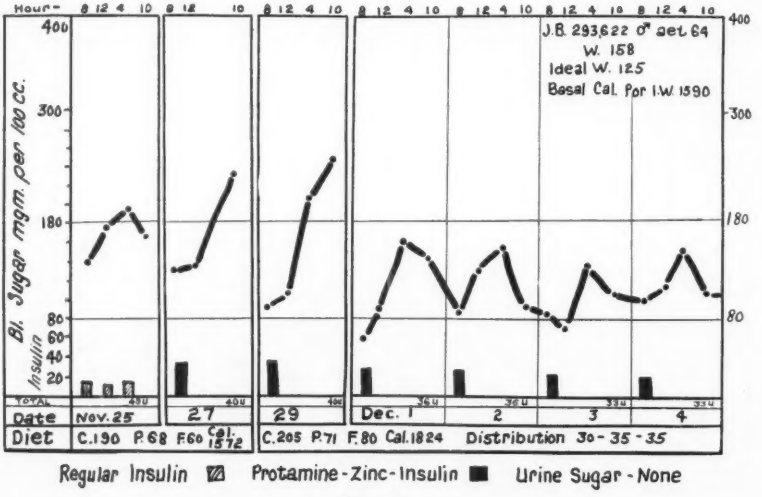

Chart 5

glycemia which followed is apparent. It is interesting to note that no insulin reactions occurred. This case demonstrates the disadvantage of attempting to make the dose of protamine-zinc-insulin equal to the required dose of regular insulin and also the difficulty involved in estimating the proper dosage where good control is not obtained prior to the change from regular insulin to protamine-zinc-insulin.

When fairly stable control is first obtained with regular insulin, an immediate substitution with protamine-zinc can usually be made. However, we feel that the doses of protamine-zinc-insulin should seldom equal

the doses of regular insulin used and in cases of moderate severity it has been our practice recently to substitute a single dose of protamine-zinc-insulin of about 80 per cent of the regular insulin requirement. In the more severe case, considerable rise in blood sugar levels during the first few days is likely to occur. During this time, glycosuria occurs but we have not seen acidosis of consequence during such a transition period. If the rise in blood sugar levels during the first two days of such a transition period tends to be excessive, it may be prevented by the addition of one or two doses of regular insulin which will not usually need to exceed more than 10 per cent of the previous requirement of regular insulin. Such accessory regular insulin may be necessary for only a few days. Within a week, further reduction in insulin dosage is often necessary and in many of our cases even after leaving the hospital, further reduction may be found advisable within a period of two or three weeks.

Chart 5 shows the blood sugar levels during a typical day of moderately good control with three doses of regular insulin, totaling 49 units. On November 27, 80 per cent of this dose, i.e., 40 units of protamine-

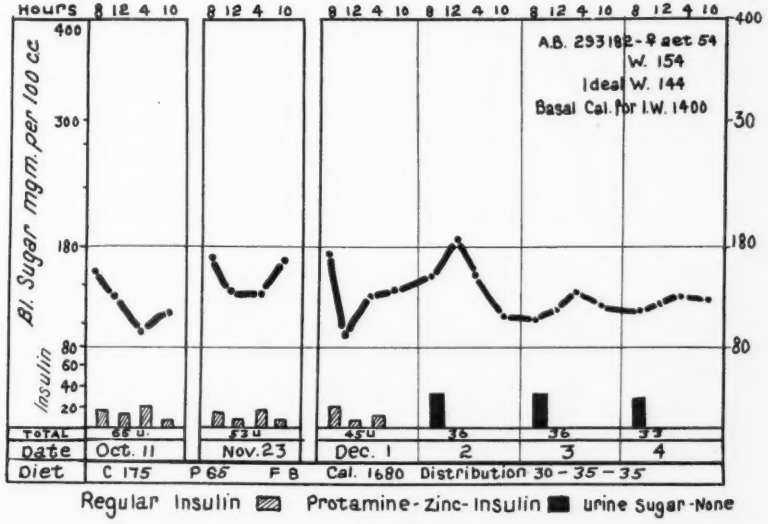
Hours 8 12 4 10 8 12 4 10 8 12 4 10 8 12 4 10 8 12 4 10 8 12 4 10
Bl. Sugar mgm. per 100 cc
400
300
180
80
60
40
20
Insulin
A.B. 29318 2-9 aet 54
W. 154
Ideal W. 144
Basal Cal. for I.W. 1400
400
30
180
80
TOTAL 65 u. 52 u 45 u 36 36 33
Date Oct. 11 Nov. 23 Dec. 1 2 3 4
Diet C 175 P 65 F 8 Cal. 1680 Distribution 30 – 35 – 35
Regular Insulin Protamine-Zinc-Insulin urine Sugar-None

Chart 6

zinc-insulin, was given as a single morning dose. The typical rise in blood sugar levels during the day for the first few days is apparent and the gradual fall in fasting blood sugar levels is also demonstrated. Subsequent reduction in dosage is shown and excellent control has followed the use of 33 units per day of protamine-zinc-insulin as compared to a less satisfactory control previously on 44 units per day of regular insulin.

Chart 6 shows several days of control on regular insulin on diminishing doses, together with a smooth transition period and subsequent excellent control beginning with 80 per cent of the regular insulin requirement with subsequent dosage reduction.

As indicated above, in mild cases where only the fasting blood sugar level remains high, this can readily be controlled by daily single doses of protamine-zinc-insulin and such control can be accomplished by doses as small as 5 units per day.

Even in severe cases, the fasting blood sugar level will be the lowest of the day and with sufficient dosage can be brought within normal range. If it is obvious, however, that the blood sugar levels during the day will not be controlled by such a dose, it will be necessary to add one or two doses of regular insulin. Such a case in which control was difficult is shown in chart 7.

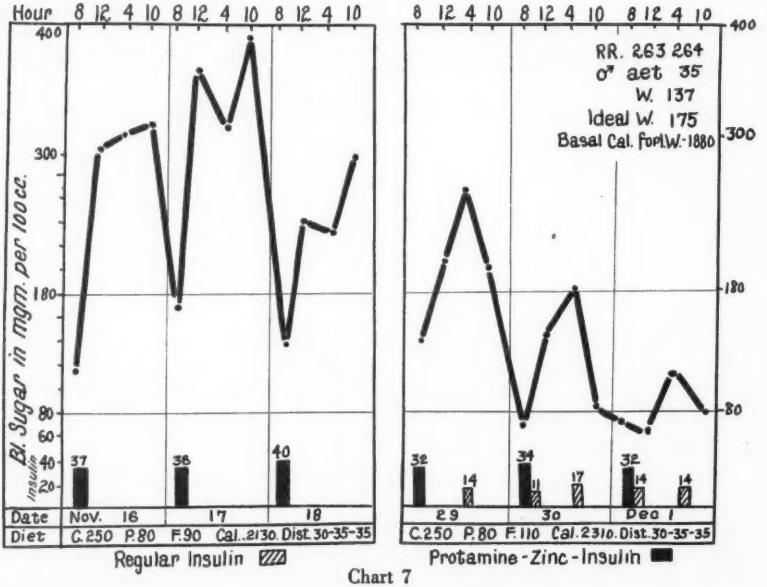

Chart 7

The general rules which we follow at present, therefore, in changing from regular to protamine-zinc-insulin may be summarized as follows:

The patient is placed on a well regulated diet and good control is obtained with regular insulin. An immediate change is then made with a single morning dose of protamine-zinc-insulin which is approximately 80 per cent of the previous requirement of regular insulin.

If the blood sugar levels during the day are excessively high, regular insulin is added to the amount of about 10 per cent of the previous

requirement of regular insulin. The dose of protamine-zinc-insulin is then manipulated in such a way as to obtain relatively normal fasting levels, changes in dosage not being made oftener than every third day. Subsequently, if morning reactions occur and if the fasting urine is sugar-free or if the fasting blood sugar levels are excessively low for two successive days, a reduction in protamine-zinc-insulin is necessary. If, on the other hand, sugar appears in the morning urine or if the fasting sugar levels remain high for more than two consecutive days, the protamine-zinc-insulin dosage may be increased. Where the fasting blood sugar levels are well regulated, one or two additional doses of regular insulin will be necessary if the blood sugar levels during the day persist at abnormal heights.

Reactions

It is a remarkable fact that with the use of protamine and protamine-zinc-insulin, the blood sugar level may reach 40 mg. or below without reactions. Reactions do occur, however, and for the most part tend to be mild and gradual in their onset, thus allowing more time for treatment. Because of the gradual onset of such reactions, it is, however, more difficult for the patient to detect an oncoming reaction. Because of the prolonged effect of protamine-zinc-insulin, the reactions themselves are likely to be prolonged and to recur after treatment. Considerable hypoglycemia may occur without pronounced symptoms. It becomes more necessary than ever, therefore, to elicit any symptoms or signs which may be evidences of hypoglycemia. This is especially true in elderly individuals or in those with arteriosclerosis, especially arteriosclerotic heart disease. Fatigue, tingling, slight disturbance of memory, irritability, slight difficulty in speech, mild nausea, or headache should be suspected as possible symptoms of hypoglycemia. I have seen only one severe reaction with a convulsion, and this occurred in a child whose symptoms of hypoglycemia were present in this instance for nearly 12 hours.

In the treatment of a protamine-zinc-insulin reaction, it is advisable to use small doses of glucose or milk, to be prepared to repeat the treatment if necessary, and to avoid the use of excessively large amounts of sugar at one time.

Reduction in Dosage and in Number of Injections

In 15 cases in this group, previous control had been good and had been maintained at a relatively stationary level for more than six months preceding the use of protamine-zinc-insulin. The average daily requirement of regular insulin had been 37.6 units while that of protamine-zinc-insulin was 22.6 units. Of the entire group, the daily dose dropped from an average of 45.5 units of regular insulin to 25.3 units of protamine-zinc.

The average number of daily injections necessary in the whole group was 2.8 on regular insulin and 1.6 on protamine-zinc. This difference appears to be increasing with experience since, in the last 16 patients treated, the use of accessory regular insulin has been found necessary in only two cases. The average daily number of injections in this smaller group was 3.1 of regular insulin and 1.2 of protamine-zinc-insulin.

Contraindications

The usually recognized contraindications are acidosis, infections, and pre- and postoperative care. Attempts are being made to determine the usefulness of protamine-zinc-insulin in these conditions but experience is not sufficient to warrant comments.

Comment

Though the advantages of protamine-zinc-insulin outweigh its disadvantages, the latter have not received much emphasis. Better control can be secured with it in many cases but regulation, especially in the severe cases, is more difficult and will require a more intelligent grasp of the problem by the physician than has been necessary before. Hospitalization for control is more important and usually will be more prolonged. The handling of the preparation is more difficult and its injection must be done with greater care. Although reactions are less frequent, if they do occur, they are likely to be more difficult to detect and more prolonged. What effect this will have in the patient with arteriosclerosis remains to be seen. Some of the early disadvantages, such as instability of the solutions and the necessity of mixing them, have already been overcome.

Against these disadvantages we have more stable control, fewer injections, and lower dosage. It is hoped that as a result of the better control there will be a diminution in the incidence of hyperlipemia, liver disease, and degenerative disorders, especially arteriosclerosis. In these respects the responsibility of the profession has increased.

Summary

Protamine-zinc-insulin in common dosage appears to be active for 50 to 65 hours after injection. Its maximum effect is usually reached in 12 to 18 hours. The prolonged effect of single daily doses makes it unnecessary to use more than one dose daily. The cumulative action increases to the third day or longer and reduces the requirment of insulin to less than 75 per cent of the dose of regular insulin in most cases. Total dosage, number of injections, and the frequency of reactions are all reduced by its use. In all cases in which we have used it thus far, control has improved. A normal fasting blood sugar level marks the limit of increase in protamine-zinc-insulin dosage. If, when this limit is

reached, the blood sugar levels during the day remain high, one or more accessory doses of regular insulin are required for control. In some mild cases, a dose of protamine-zinc-insulin every second or third day may be sufficient to control fasting sugar levels.

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CLINICAL NUTRITIONAL DEFICIENCY DISEASE

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It is increasingly evident to clinicians that a lack of necessary specific nutritional elements often leads to definite symptoms and syndromes. Certain deficiency diseases such as scurvy and beriberi resulting from a total lack of such elements have long been recognized but are seldom seen in this country. Mild symptoms, however, due to an inadequate supply of nutritional factors occur frequently. We should think of a nutritional deficiency state as a combination of different symptoms and signs resulting from the disturbed nutrition of tissue rather than as a definite "disease." Often, more than one specific element is lacking, thus further complicating the picture. A nutritional deficiency results from a deficient supply or use of a specific nutritional element at the point of normal utilization. The element may be brought by the blood stream to the point of normal utilization and still be unused. Thus, in certain conditions such as lead poisoning, iron may be supplied in adequate amounts without influencing an iron deficiency anemia because the tissues are unable to utilize the iron offered in the building of hemoglobin. Similarly, absorption may be interfered with so the nutritional element is of no more value so far as the tissue needing it is concerned than if it had not been taken into the gastro-intestinal tract. It is apparent also that vomiting and diarrhea cause a mechanical loss of elements before absorption can take place.

All the specific nutritional elements must be ingested as such or formed in the gastro-intestinal tract from ingested food. The vitamins and mineral salts are taken in preformed, while other elements represent altered food constituents. Thus, the substance protective against pernicious anemia is formed by the interaction of something supplied by the stomach, the intrinsic factor, on something contained in ingested food, the extrinsic factor. Further study will probably reveal other factors similarly formed from intrinsic and extrinsic factors, but the erythrocyte maturing factor is the only one so far proved. The more important specific nutritional elements now known are: (1) calcium, (2) iron, (3) vitamin A, (4) vitamin B_1, (5) vitamin B_2 complex, (6) vitamin C, (7) vitamin D, and (8) the erythrocyte maturing factor (EMF) protective against pernicious anemia.

I have summarized in the following table the now accepted essential functions of the more important specific nutritional elements and indicated the "disease" recognized as due to a total lack of each element. We are especially interested, however, in the minor symptoms of the deficiency "state" rather than the fully developed deficiency diseases (Table I).

TABLE I
NUTRITIONAL FACTORS WITH A SPECIFIC FUNCTION

Factor	*Specific Function*	*Clinical Signs of Deficiency*	*Clinical Syndrome ("disease")*
Calcium	Necessary for the normal function of bone and nerve tissue.	Increased nerve irritability.	Tetany.
Iron	Necessary for the formation of hemoglobin and erythrocytes.	Anemia of hypochromic and often microcytic type.	Hypochromic anemia
Vitamin A	Necessary for the integrity of epithelial tissue.	Epithelial defects.	Ophthalmia; urinary calculi; night blindness.
Vitamin B_1	Necessary for the integrity of nerve tissue.	Anorexia; neuritis; edema.	Beriberi; multiple neuritis.
Vitamin B_2 complex	Necessary for the integrity of dermal tissue.	Glossitis; dermatitis; neuritis; mental disturbances.	Pellagra?
Vitamin C	Necessary for the integrity of the endothelium of blood vessels.	Hemorrhage due to vascular defects.	Scurvy.
Vitamin D	Necessary for the normal metabolism of bones and teeth.	Softening of bone; decay of teeth.	Rickets; dental caries.
Erythrocyte maturing factor (EMF)	Necessary for the maturation of erythrocytes in bone marrow.	Glossitis; diarrhea; anemia of macrocytic type; degeneration of spinal cord.	Pernicious anemia; subacute combined degeneration of spinal cord; sprue.

The formation, absorption or use of specific nutritional elements in the body is influenced greatly by numerous conditions, the more important of which are:

(1) Insufficient intake of food.
(2) Absence of some digestive factor necessary for the formation of a specific nutritional element for food (as the intrinsic factor lacking in pernicious anemia).
(3) Excessive loss of gastro-intestinal contents by diarrhea or vomiting.
(4) Increased need, as in pregnancy and lactation or states of overactive metabolism as hyperthyroidism.
(5) Presence of any toxic state impairing absorption and utilization such as malignancy or poisons as from lead, renal insufficiency, or infection.
(6) Anemia in which there is a deficient interchange between oxygen and food and tissues.
(7) Achlorhydria which affects the absorption or production of specific factors from food.
(8) Lowered metabolism in which the tissues are working at an abnormally low speed.
(9) Impaired glucose tolerance which seems to increase the need or impair the use of at least some of the nutritional elements.
(10) Disturbed circulation.

This is a large group of influencing factors, but each must be evaluated in any consideration of "deficiency" disease.

Illustrative Cases

Edema Due to Vitamin B Deficiency

Case 1: An attorney, 27 years of age, complained of edema beginning one week before admission without other significant symptoms. The gain in weight during this week had been 16 pounds. During the preceding two years, the patient had reduced his weight from 165 to 105 pounds by diet restriction for furunculosis. The diet consisted with very little variation of grapefruit and a small portion of meat daily and lettuce occasionally. .

On examination, the weight was 127 pounds. The edema was generalized. There was no muscle weakness, change in tendon reflexes, or sensory disturbance. The pulse rate was 60, the blood pressure 100 mm. of mercury systolic and 64 diastolic. There was no anemia, and repeated urinalyses revealed no abnormalities except a low specific gravity. The urea clearance test showed 67 per cent of normal and the phenolsulphonphthalein excretion was 65 per cent in 2 hours. It was evident from the examination that no cardiac or renal factor was responsible for the edema. A hypoproteinemia was also excluded since the total blood proteins were 6.74 per cent with 3.97 per cent albumin and 2.77 per cent globulin.

The clinical diagnosis was edema due to vitamin B deficiency, and a high vitamin diet with a vitamin B concentrate was prescribed. In three weeks, the edema entirely disappeared with a loss in weight of 16 pounds. The patient had been symptom-free for four months when the edema recurred following discontinuance of the concentrate. The serum protein at this time was 8.3 per

cent. The edema again disappeared. With a normal diet, the patient has been symptom-free for three years.

In this case, the important element in the development of the deficiency state was evidently the deficient intake of protective foods. At the time of the original examination, the basal metabolic rate was minus 26 per cent. This has been observed repeatedly and always found to be low. The lowered rate was probably an influencing factor in the development of the disease.

Weakness Due to Vitamin B Deficiency

Case 2: A housewife, 38 years of age, complained of weakness and shortness of breath on exertion for four years and weakness of the left leg for two years. She had been perfectly well until the birth of a third child (weight 11 pounds) five years before this examination. She had always been very active, but now noticed extreme weakness and dyspnea which permitted her to walk only one or two blocks without resting. For two years, the left leg had been very weak and for the past few days, the patient had been unable to get out of bed without assistance. She had consulted many doctors without relief. There were no other significant points in the history except marked constipation which had been present for years. She had lost 20 pounds in weight during the preceding six months.

Examination revealed that the patient weighed 152 pounds (the normal for her age and height being 138 pounds), the blood pressure was 120 mm. of mercury systolic and 90 diastolic. There was no infection. A complete general examination and a special neurological examination showed no objective findings except absent Achilles tendon reflexes. The tongue was smooth and rather atrophic. A gastric analysis made before admission had shown an achlorhydria. The basal metabolic rate was plus 2 per cent, the Wassermann test gave a negative reaction, and the blood sugar tolerance curve was normal. Roentgen examinations of head, chest, and gastro-intestinal tract all gave negative findings except for the colon. This was enormously dilated and very redundant. There was no anemia.

During observation in the hospital, the pulse rate was rapid and after walking only 30 seconds it rose to 160. The temperature was normal. The weakness was so extreme that the patient could not step on a scale platform without help. With no other treatment except a high vitamin, low carbohydrate diet and added vitamins, improvement was rapid so that she could walk the length of the corridor without assistance within two weeks. Two months later, she returned to show that all symptoms had disappeared entirely. Her weight was 140 pounds, all the deep tendon reflexes were normal, and a barium enema showed a great decrease in the size of the colon.

So far as could be ascertained from the history, this patient had followed an average normal diet. Her symptoms followed a pregnancy. She had an achlorhydria and a very abnormal colon. The abnormality of the gastro-intestinal tract was probably an important factor in the impaired absorption or use of the protective foods, although McCarrison[1] has shown experimentally that loss of tone and dilatation

of the gastro-intestinal tract occurs commonly in the presence of vitamin B deficiency, so this may be a result rather than a cause.

Kidney Stone Due to Vitamin A Deficiency

Case 3: A man, 49 years of age, gave a history of passing renal calculi for 18 years, and several attacks of hematuria had occurred during the year preceding our examination. He had limited his food for a long time on account of indigestion. His diet for years had been as follows: breakfast—coffee and whole-wheat toast; lunch—soup, tea, and lemon; dinner—meat and two vegetables in small amounts. This patient weighed 170 pounds and his height was 69 inches.

The general examination was entirely negative. The blood pressure was 140 mm. of mercury systolic and 94 diastolic. A roentgenogram of the kidney showed a small stone in the right kidney pelvis. There was no anemia. Examination of the urine showed a few red cells and a trace of albumin, but there was no gross blood. It was alkaline in reaction with a pH of 7.8. The retinal sensitivity as measured by the biophotometer test was much diminished. Following use of the acid-ash high vitamin A diet, the pH of the urine fell to 4.8.

Atypical Scurvy Due to Vitamin C Deficiency

Case 4: A man, 58 years of age, was seen at the Clinic in October, 1933, with a typical history of duodenal ulcer, and gastric retention was demonstrated by roentgen examination. The patient had followed a stringent Sippy regime for two years and had taken no fruits except prunes, although he had been instructed to drink juice of citrus fruits. All the gastric symptoms disappeared, but two years later, the patient returned because a large hemorrhage had developed about the elbow and another in the lip without apparent cause or injury.

The general examination was negative except for one infected tooth. There were no petechiae although the tourniquet test was positive. A special examination of the blood for hemorrhagic disease showed no anemia or abnormality of the white cells. The platelets numbered 280,000 with normal clot retraction. The bleeding time was one and one-half minutes. The coagulation time was 20 minutes (normal 5-10 minutes). With a diet high in vitamin C, all symptoms disappeared rapidly.

Peripheral Neuritis Due to Lack of Vitamin B_1 and Hypochromic Anemia

Case 5: A woman, 46 years of age, was first seen because of menorrhagia which had been present during the preceding six months and which was found to be due to a cancer of the cervix. She tired easily, was dyspneic on exertion, and had edema of the feet. The examination was entirely negative except for the malignancy and a marked anemia. The red blood cells numbered 3,130,000 and the hemoglobin content was 45 per cent. The cancer responded to radium therapy and there had been no sign of recurrence or metastasis. While the patient was in the hospital, iron was given and the hemoglobin content of the blood had risen to 68 per cent six weeks after admission.

Eight months later, the patient returned complaining of severe pain in the hands and feet which had been severe enough to wake her at night. Neurologic

examination revealed no paresthesia or other abnormality. She had gained 11 pounds in weight at the time she had edema of the feet. No further blood loss had occurred since the radium therapy. She had always taken very little meat and had eaten excessively of sweets.

She now showed marked atrophy of the tongue, blue sclerae, and the spoon nails characteristic of idiopathic hypochromic anemia. The blood count showed 4,760,000 red cells with 46 per cent hemoglobin and a volume index of 0.6 per cent.

Peripheral Neuritis, Dental Caries, and Hypochromic Anemia Due to Deficiency in Vitamin B_1 and Iron

Case 6: A woman, 22 years of age, was admitted in the sixth month of the fifth pregnancy in five years. Six months previously, numbness and weakness of the hands and feet developed and this progressed to complete motor paralysis of all extremities. The deep reflexes were absent and no sensory changes were found. There was marked muscle atrophy. The tongue was smooth and red. Edema was absent. There were marked dental caries. The spinal fluid was normal. Free acid was absent in the stomach and the total acidity was only 31. Examination of the blood showed: red cells, 3,950,000; hemoglobin, 68 per cent; color index, 0.84.

This patient was the wife of a steel mill worker and her diet had been limited for economic reasons. Five pregnancies had occurred in rapid succession and with each, she had had marked vomiting. With a balanced diet to which vitamins and iron were added, the pregnancy proceeded normally and the patient has made a complete recovery.

Sprue, Peripheral Neuritis, Macrocytic Anemia, Tetany, Deficiency in Erythrocyte Maturing Factor (EMF), Vitamin B, and Calcium

Case 7: A man, 26 years of age, had been treated for pernicious anemia for two years. On admission, he had a constant diarrhea with large stools, excessive formation of gas, and weakness. For one year he had had marked numbness of the hands and feet.

On examination the tongue was smooth and a test meal showed no free hydrochloric acid. There were no neurologic findings of significance. Examination of the blood showed a macrocytic anemia with a volume index of 1.44. The red cells numbered 2,940,000 and the hemoglobin content was 78 per cent. With intramuscular liver therapy, the diarrhea ceased and the blood returned to normal. While in the hospital, a typical carpopedal spasm of tetany developed which was relieved by the intravenous injection of calcium. The blood calcium was as low as 8.64 mg. per 100 cc.

This patient had a macrocytic anemia and sprue due to a deficiency in the erythrocyte maturing factor, a deficiency neuritis, and a calcium deficiency, all of which were relieved following liver therapy.

Pellagra and Pernicious Anemia (Deficiency in Vitamin B_2 and the Erythrocyte Maturing Factor)

Case 8: A single woman, 60 years of age, had been losing weight for three months and had become increasingly weak and mentally dull. She had been confined to bed for one week. Pallor and dryness of the skin had been noticed

for some time. On admission, the patient was confused and answered questions with difficulty. She was obese; the face and legs were edematous and the dorsum of the hands showed marked wrinkling and scaly dermatitis. Over the elbows, the skin was markedly pigmented. There were no significant neurologic findings and no glossitis or stomatitis. The urine and blood proteins were normal. The blood showed a macrocytic anemia with a red cell count of 2,990,000, hemoglobin content of 65 per cent, and volume index of 1.21. The test meal showed an achlorhydria.

In the hospital, the patient had a daily rise in temperature to as high as 102° F. without apparent cause except the deficiency disease. With high vitamin feeding and the administration of liver extract intramuscularly, the edema disappeared and the mental state returned to normal.

This patient had a macrocytic anemia with achlorhydria typical of pernicious anemia and the skin and mental changes seen in well developed pellagra, and responded to liver therapy.

These case histories illustrate various phases and combinations of nutritional deficiency disease. Certain symptoms and signs should always suggest the possibility of a specific nutritional defect: a macrocytic anemia suggests a deficiency in the erythrocyte maturing factor (EMF) and a hypochromic anemia a deficiency in iron. Hyperirritability of the neuromuscular mechanism may be due to a lack of calcium. Night blindness, pyorrhea alveolaris, ophthalmia, and urinary calculi should bring to mind vitamin A insufficiency. Disturbances of the peripheral nerves suggest a vitamin B_1 deficiency just as dermatitis, pigmentation of the skin, glossitis, and stomatitis with mental disturbances suggest a vitamin B_2 complex deficiency. Rickets and dental caries suggest a vitamin D deficiency, while easy bruising and unexplained edema suggest a deficiency in vitamin C. It is most important to remember that deficiency disease may arise when the patient seemingly is ingesting a normal amount of the specific principle; this is due to interference with absorption or utilization by one or more of the numerous influencing factors mentioned above. To keep in mind the possibility of deficiency disease is often to solve an obscure clinical problem.

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CALCIUM CARBONATE BILE

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Calcium carbonate bile, or "milk of calcium bile" as it is sometimes referred to, is a condition in which the bile becomes heavily loaded with calcium carbonate and is opaque to the roentgen ray. Because it may be mistaken for a normally functioning gallbladder and because of its relative infrequency, the following case, which presents the typical signs and findings usually found in such a condition, is reported.

The patient was a married, white woman, thirty-one years of age, who was a housewife. The chief complaint was pain in the stomach which had occurred at intervals for the two years previous to our examination. She stated that about two years ago she began to have attacks of cramp-like pain in the epigastrium, which came on after eating and were relieved by vomiting. The attacks were rather frequent at first and lasted for several hours, but were not accompanied by chills or fever. During the preceding year, the attacks had been more frequent and more severe, with continuous vomiting during these times and with inability to retain either food or water. These attacks were not related to the ingestion of food nor to the time of day. The pain was confined chiefly to the epigastrium, but at times it radiated through to the back between the shoulders and often was so severe that a hypodermic would be required to give relief. The patient had been constipated for the past ten or twelve years and used some type of laxative daily. She had noticed that the stool was very light in color at times but there had been no diarrhea or blood in the stools. For the five days preceding our examination, the pain had been very severe and almost constant. A weight loss of fifteen pounds had occurred during the past several months.

The family and past history were essentially negative. The father, mother, and husband were living and in good health; one child was living and well and there was no history of miscarriages. The patient had had no illness except the usual childhood diseases. There had been no symptoms referable to the chest, cardiovascular or genito-urinary systems.

Physical examination revealed a thin, underweight, asthenic woman. The skin was moist and warm with no evidence of jaundice. The eyes were normal except for a slight icteric tinge to the sclera. The tonsils were small, ragged, and embedded; otherwise the mouth and pharynx were normal. The chest was symmetrical and showed good and equal expansion. The lungs were resonant throughout with no râles. The heart was of normal size, shape, and position. The heart sounds and rhythm were normal and there were no murmurs. The abdomen was scaphoid with no masses or spasticity. Tenderness was elicited by pressure over the gallbladder area and over the course of the colon in the right lower quadrant; the tenderness over the gallbladder, however, was the most definite. The remainder of the physical examination gave entirely normal findings.

Laboratory findings: The specific gravity of the urine was 1.024 and there was no albumin, sugar, casts, red or white blood cells. Examination of the blood showed 4,500,000 red cells, 5,000 white cells, and 84 per cent hemoglobin. The blood urea was 24 mg., blood sugar, 79 mg., blood cholesterol, 240 mg., blood calcium, 10.3 mg., and phosphorus, 2.3 mg. per one hundred cubic centimeters of blood. Both the Wassermann and Kahn tests gave negative reactions.

FIGURE 1: Plain film showing shadow simulating a normally functioning gallbladder.

The Ewald test meal showed a free acid of 8 and a total acid of 17. A quantitative examination of the contents of the gallbladder after operation showed iodine to be present to the extent of 5.2 gamma per 100 mg. while the calcium content was 9.2 per cent.

Clinical impression: Chronic cholecystitis and lithiasis; spastic colon; visceroptosis.

Roentgen examination: A roentgenogram of the kidneys, ureters, and bladder showed the lumbosacral spine to be normal, with no suspicious

shadows in the urinary tract. The gallbladder was opaque and well visualized. The right kidney was normal in size, shape, and position. The left kidney was not visualized.

Plain films showed good visualization of the gallbladder and no change was seen after ingestion of the cholecystographic dye. The gallbladder changed shape after a fat meal. The stomach, duodenum, and colon were normal.

Operation: Cholecystectomy and appendectomy were performed under avertin analgesia and ether anesthesia. The common duct was not dilated and no stones could be palpated in it. The duodenum was apparently normal.

Pathological report: The gross specimen consists of a gallbladder and an appendix. The gallbladder measures 10 cm. in length and 2.5 cm. in width. The serosal surface is smooth and pinkish-gray. The wall is moderately thickened. The mucosa is pinkish-gray and granular. Obstructing the cystic duct is a mulberry-shaped calculus measuring 0.6 cm. in diameter. It is soft and is apparently composed of calcium and cholesterin. Free in the lumen of the gallbladder are two similar stones measuring respectively 0.4 and 0.3 cm. in diameter. There is a considerable amount of concentrated bile which has the consistency of soft putty.

Microscopic sections of the gallbladder show thickening of the wall, enlarged mucosal glands, mild inflammatory reaction in all the coats, and fibrosis of the adventitial coat.

Pathological diagnosis: Chronic cholecystitis; cholelithiasis; chronic appendicitis.

The gallbladder as it was first seen during the roentgen examination is shown in figure 1, which is the plain film of the kidneys, ureters, and bladder. This film is made as a routine procedure in all our examinations of the gastro-intestinal tract and is made the day before cholecystographic dye is given. The gallbladder is seen very distinctly on this film and appears much as a normal gallbladder does after cholecystographic dye is administered. The film made 15 hours after ingestion of dye is seen in figure 2. The gallbladder shadow is no more dense here than in the plain film, although the outline has changed somewhat. A fat meal was given this patient but no change in the size of the gallbladder was seen on the film made after the meal.

The diagnosis in this case is quite evident, but a differentiation must be made between opaque bile, a large opaque calculus, and calcification in the wall of the gallbladder. A positive diagnosis of opaque bile may be made if the shape of the gallbladder is seen to change, either on the different films or more especially after the fat meal. Calcification in the wall of the gallbladder generally shows as heterogeneous areas of varying densities, and these shadows will always remain constant in their position.

Calcium carbonate bile, while not rare, is relatively uncommon. Several authors have reported cases similar to ours but we have seen only one report of the frequency with which it may be expected.

FIGURE 2: Cholecystogram after administration of dye. No change is seen in the density of the gallbladder shadow.

Mathews, in a discussion of a paper by Phemister et al[1], stated that, in the examination of 6700 gallbladders, he had recognized only one of this sort. We have found this condition to be more common, however, since in the last 1700 examinations of the gallbladder which have been made at the Cleveland Clinic, we have seen two which contained opaque bile. One of these, the present case, was proved at operation. Operation

has not yet been performed in the second case, but the same findings were revealed in a subsequent recheck examination of the gallbladder.

The chemical analysis of the contents of the gallbladder in this case is interesting, since in other reported cases we have not seen a quantitative report of the amount of calcium present in the thick, putty-like substance. In some of these cases it was simply reported that a high percentage of calcium was found. In the case under consideration the calcium content of the dried mass was found to be 9.2 per cent. The total amount of inorganic salts in normal bile is about 0.65 per cent, which includes other compounds as well as calcium. It is readily seen that in the contents of this gallbladder there is a tremendous increase over the normal amount of calcium, thus accounting for the very dense gallbladder shadow which was seen in the original plain film. A roentgenogram of the surgical specimen is shown in figure 3, the gallbladder having been opened and the calculi and calcium carbonate removed. The opaque nature of the bile in comparison to the density of the calculi and the gallbladder itself will be noted. A qualitative chemical examination of the thickened bile was not made since it is quite generally conceded that the calcium salt found in these cases is calcium carbonate.

The formation of calcium gall stones and the thick milk of calcium bile are probably very closely related. Since, in this case and others reported, there has always been an obstruction of the cystic duct, it would seem that this is a necessary factor for the formation of calcium products within the gallbladder. The obstruction in most cases has been due to a calculus, although any obstruction, such as may be the result of a neoplasm, will produce a similar result.

When the obstruction of the duct is established and a certain amount of infection is present, there is a thickening of the gallbladder wall with a subsequent change in its physiology. With these changes, there probably occurs an increase in the excretion of the calcium-bearing mucus from the walls of the gallbladder. Certainly, obstruction of the cystic duct alone is not sufficient to cause this condition, as is shown by those cases of obstruction and hydrops in which no increase in the calcium content is noted. It would seem, then, that the correct amount and severity of inflammation and obstruction must be present before calcium-containing substance is formed within the gallbladder.

Various attempts have been made to reproduce such phenomena. Wilkie[2] was able to produce both calcium and the cholesterol calculi in rabbits. In his experiments, cholecystitis was induced in each animal, and in some the cystic ducts were ligated. He found that if the cystic duct were not obstructed, cholesterol calculi resulted, whereas, if the cystic duct were ligated, stones rich in calcium were produced.

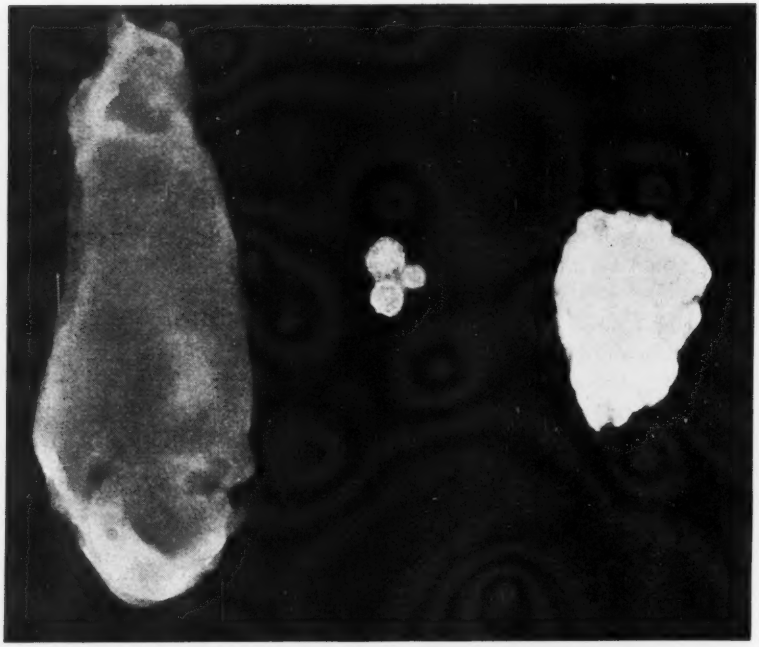

FIGURE 3: Roentgenogram of opened gallbladder and contents.

The acidification of the bile in the gallbladder is perhaps one of the important factors which prevent the formation of calculi within the gallbladder. The hydrogen-ion concentration of bile in the normal liver is 8.2, while that in the gallbladder ranges from 5.8 to 6.0 and is strongly acid to litmus. The solubility of any salt, calcium carbonate as an example, is certainly influenced by the fluid in which it is contained. In the acidified bile the calcium is not precipitated; hence no calcium stones are formed. On the other hand, if any process, such as an inflammatory change in the gallbladder wall, interferes with or changes the normal physiology, we may expect the bile to become more alkaline and to approach the hydrogen-ion concentration of liver bile. This would be a factor favoring the precipitation of calcium and the formation of opaque calculi or calcium carbonate bile.

The possibility of the presence of opaque bile is of major importance to the roentgenologist if he is to avoid error in the interpretation of cholecystograms. The roentgen examination must be complete and should include plain films as well as the usual films made after the ingestion of the gallbladder dye. In the case under discussion, the gallbladder was so well visualized on the plain film that one might easily

believe it to be a normally functioning gallbladder containing dye and to report it as such.

The fat meal is of value in certain cholecystographic examinations to rule out shadows of the gallbladder and to differentiate between calcification in the wall or the presence of opaque bile as in the present case.

The formation of calcium carbonate bile is probably dependent upon a combination of obstruction and inflammatory changes, with a subsequent change in the physiology of the gallbladder.

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SILICOSIS

A. Carlton Ernstene, M.D.

Although excellent discussions of the clinical, roentgenologic, and pathologic aspects of silicosis are available in the literature, accurate knowledge of the characteristics of the disease has not yet been widely diffused. Because of this and because the industrial and medicolegal importance of silicosis is constantly increasing, it seemed that a report of a typical case and a brief discussion of the more important features of the disease should be of interest.

Report of Case

The patient, a white man, aged 56 years, had experienced frequent attacks of bronchitis during the winter months for more than twenty years. Fifteen years ago he had had a persistent productive cough which was accompanied by low-grade fever, night sweats, weakness, and a loss of 20 pounds in weight. A diagnosis of pulmonary tuberculosis was made, but the patient did not know whether tubercle bacilli were found in the sputum. A daily elevation in temperature to 100° or 101° F. had persisted for several months, and for the next three years the patient had spent practically all his time resting. He had then taken up farming and had been able to do hard work although a productive morning cough continued and strenuous exertion always caused definite dyspnea. He had continued to have frequent "colds" during the winter months, and of late years these had been accompanied by severe attacks of wheezing which were relieved by the subcutaneous administration of epinephrine. The weight which had been lost at the onset of the illness had never been regained.

Three weeks before coming to the Clinic the patient had experienced an acute infection of the upper respiratory tract and since that time he had been unable to work because of dyspnea, cough, and general weakness.

Between the ages of 14 and 41 years the patient had been employed continuously in a stove works making large molds from sand.

Physical examination revealed a well developed but rather poorly nourished individual who experienced moderate dyspnea upon such slight exertion as undressing and dressing. There was no cyanosis. The pupils reacted normally. The thorax was symmetrical and the respiratory movements were equal on the two sides although diminished in extent. The breath sounds were diminished and expiration was prolonged throughout both lungs. Rhonchi were present in all lung fields, and numerous medium moist râles were heard over both bases. The heart was not enlarged and its rate and rhythm were normal, but all sounds were somewhat faint. The arterial blood pressure was 115 mm. systolic and 80 mm. diastolic. Examination of the abdomen and of the extremities revealed nothing abnormal.

Urinalysis and blood counts gave normal results. The erythrocyte sedimentation rate was moderately elevated above the normal. Four specimens of sputum were examined and no tubercle bacilli were found.

Roentgenologic examination of the chest (Fig. 1) showed extensive nodular mottling throughout both lungs characteristic of silicosis. The individual nodules were discrete and sharply circumscribed and for the most part were between 2 mm. and 4 mm. in diameter. All lung fields were involved although the most extensive changes were present in the mid-portion on either side.

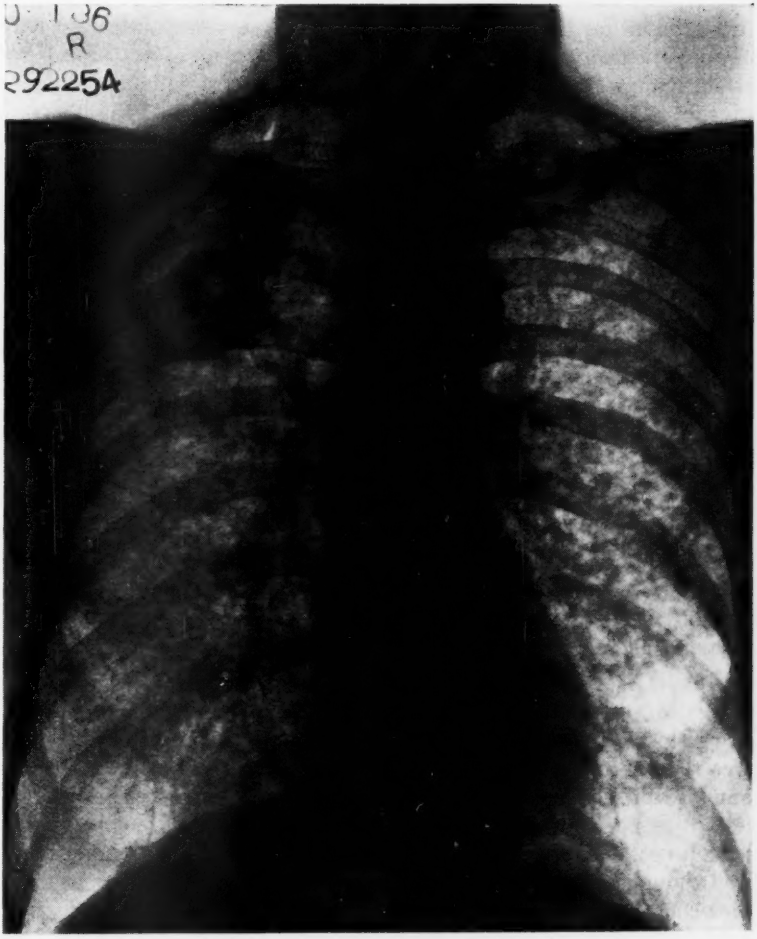

FIGURE 1: Roentgenogram of the chest.

In addition to the generalized mottling, the upper lobe of the right lung contained an area of fairly uniform infiltration which measured 6 cm. by 4 cm. in its greatest diameter. The upper lobe of the left lung contained two similar areas which were circular in outline and measured 2.5 cm. and 1.4 cm. respectively in diameter.

DISCUSSION

Silicosis results only from the inhalation of free silica (silicon dioxide). All other dusts, with the exception of asbestos, are quite harmless; they may cause pigmentation and slight proliferation of

fibrous tissue in the lungs but they do not in any way interfere with pulmonary function. Asbestos is a hydrated magnesium silicate of variable composition and causes a type of pulmonary pathology entirely different from silicosis. Silicon dioxide is encountered in industry in several different forms, most commonly as sand, sandstone, tripoli, quartz, quartzite, flint, and diatomaceous earth.

The development of silicosis is governed by a number of factors, the most important of which are: (1) the size of the inhaled particles of silica, (2) the intensity of exposure to silica particles of suitable size, and (3) the duration of exposure. In order to reach the air spaces of the lungs and become of importance pathologically, particles of silicon dioxide must be less than ten microns in diameter. The silica content of dust to which a worker is exposed may vary from extremely low to as high as 99 per cent. Usually exposure to silica-containing dust must extend over a period of 10 or 12 years before evidence of silicosis develops. Occasionally, however, extreme exposure may result in the appearance of the disease within 2 or 3 years.

The exact manner in which silica produces harmful effects in the lungs has not been determined. The earlier belief that the pathologic changes were due to the mechanical action of particles of silica has been discarded, and it is now believed that silica acts as a tissue poison through a chemical or a physico-chemical action.

Silicosis is characterized by the occurrence of fibrosis about the lymphatic vessels of the lungs and the development of nodules of fibrosis in the lymphoid tissue. It is this latter nodular fibrosis which gives rise to the pathognomonic roentgenologic findings in the disease, namely diffuse granular mottling throughout the lungs. The development of this mottling is preceded by an increase in the linear markings in the lungs, but these earlier changes are not of diagnostic importance. Even though a person may have a history of prolonged exposure to silica-containing dust, a diagnosis of silicosis cannot be made until roentgenologic examination reveals discrete, nodular fibrosis throughout the lungs. Roentgen examination of the patient with silicosis may also reveal large areas of increased density in the lungs, as was true in the present case. According to Gardner[1] these shadows may be due either to conglomerate lesions of uncomplicated silicosis or to silico-tuberculosis. Differentiation of the two may be extremely difficult.

In the early stages of silicosis the patient appears well and has few or no complaints. When symptoms develop they consist most commonly of dyspnea, cough, and susceptibility to infections of the upper respiratory tract. Dyspnea on exertion frequently precedes all other symptoms by a considerable length of time and usually dominates the clinical picture, progressing gradually in severity until the patient is

prevented from carrying on any work. The cough is usually unproductive although exceptions to this are not rare. Fever and loss of weight are seldom present in uncomplicated cases; when they do occur they usually are the result of tuberculosis or some other complicating disease of the respiratory tract. Physical examination is of little assistance in diagnosis although more or less marked limitation of the respiratory movements of the thorax is present and the breath sounds may be greatly diminished.

Perhaps the two most important clinical features of silicosis are its tendency to progress even though the patient is removed from a dusty occupation and the great frequency with which the disease is complicated by pulmonary tuberculosis. Tuberculosis is by far the most common cause of death in patients with silicosis, and once evidence of tuberculosis appears, the illness usually runs a rapid course.

The case history summarized above illustrates a number of the most important features of silicosis, including the roentgenologic aspects of the disease, the symptomatology, and the prolonged, slowly progressive course in spite of removal from exposure to silica dust. A diagnosis of complicating pulmonary tuberculosis could not be substantiated in this patient, and it is our opinion that the larger shadows in the lungs were due to conglomerate lesions of simple silicosis. Repeated examinations will be necessary, however, before a final decision upon this point can be made.

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THE RELATIVE RÔLES OF RADIUM AND ROENTGEN RAYS IN THE TREATMENT OF CARCINOMA OF THE UTERINE CERVIX

U. V. PORTMANN, M.D.

In order to appreciate the relative rôles of radium and roentgen rays in the treatment of carcinoma of the cervix, the biologic reactions of tissues to the rays and also the physical properties of each type of radiation must be taken into consideration. From the standpoint of therapeutics, roentgen and radium rays in equal intensities produce the same biologic reactions and have the same physical properties. It has not yet been proved that there is any difference in biologic reactions between the two which might be dependent upon the quality of the rays (i.e., wave length) that cannot be explained on a purely physical basis. Really the only difference is that radium may be applied directly to neoplasms as a point source of radiation within the tumor or organ, while the roentgen rays must be directed from an external source and cover a larger field. Each, therefore, has its individual limitations and indications.

The biologic reactions which are produced by irradiation of neoplastic or normal tissues depend upon the intensity of the radiation with the added factor of the period of time over which irradiation takes place. The factor of time is important both from a clinical and physical standpoint; for example, small amounts of radium or roentgen rays over a long period do not have identical physical or biological effects as a large amount in a short time, and the histologic changes seen in the irradiated tissues are not the same under these two circumstances.

The normal skin has been taken as a biologic unit or standard of applied radiation intensity and as a basis for determining the biologic effects of radiation or for making comparisons of the reactions of tissues to different intensities. That intensity of radiation which will produce a redness of the skin in three weeks has been called a unit skin dose or an erythema dose. Thus when malignant tissues are irradiated, it is found by microscopic study after the period of reaction, that if less than 80 per cent of this unit skin dose has been given, there is little if any evidence of change. When as much as 150 per cent of this quantity is administered, there are changes which are manifested by endarteritis, increase of the fibrous tissue, and hyaline degeneration, but there is little direct permanent damage to the malignant cells, although some of them may eventually undergo starvation by the pressure of localized fibrous tissue. Much larger doses are required to produce marked fibrosis and degeneration of tumor cells by fragmentation of their nuclei. Hence, in order to eliminate malignant tissue by irradiation, it is necessary to administer a dose which is great enough to produce the

maximum effects on the neoplastic cells, and also cause sufficient reaction in the bed of tissue in which the neoplasm is growing. These manifestations of reactions in the neoplastic tissues are brought about by two factors: first, the direct destructive effect of the rays on the nuclei of neoplastic cells, and second and of equal importance, the reactions which are created in the tissue bed of the host. These reactions of the tissue bed are also brought about by two factors, the first being the normal physiologic response of the host to any degenerative process which may exist in the tissues and the second is the influence of the irradiation in altering the normal reaction to degenerative processes which are produced by the destructive effect of the rays.

The complex processes which make up the normal physiologic responses to neoplastic growths are not yet understood. The fact that such reactions do exist may be illustrated by a few examples of how the physiologic processes of the individual alter the course of malignant diseases. A young individual succumbs to a certain type of malignant growth while an older person with apparently exactly the same disease may survive for a long period. Then, too, a pregnant woman with carcinoma of the cervix or one with carcinoma of the lactating breast is doomed because her physiologic processes are producing a growth stimulus which also stimulates the growth of the malignant neoplasm. Also, when acute inflammation exists in or around a neoplasm, the influences which are established to resist the inflammation interfere with those restraining the growth of the neoplasm, which develops more rapidly than it would in uninflamed tissues. Therefore, in treating any malignant growth by irradiation, the physiologic processes of the patient must be considered. Treatment must be directed not only toward direct destruction of the neoplasm but also toward preserving and aiding the restraining influences which normally are present.

It has been found by experiments in vitro that there is a specific dose of radiation which completely destroys any malignant tissue but if less than this dose is given, there is a proportionately diminished effect. This observation is substantiated by the findings of changes which are produced by different intensities. For small doses, the changes are more or less transient with increasing degeneration and the production of fibrous tissue as the intensity of radiation is increased. However, these experiments with tissues in vitro do not explain the effects which are sometimes observed when malignant tissues are treated in vivo and when physiologic processes are exerting their influence on the neoplasm. According to the experimental evidences in vitro, the destruction of most carcinomatous tissue requires very large doses of radiation; however, every radiologist has had the experience of treating a carcinoma with a comparatively small dose, which he knows would be insufficient ordinarily, only to observe an astonishingly rapid disappearance of

the growth. On the other hand, the administration of very large doses which should ordinarily eradicate neoplasms may be entirely ineffective.

The clinical evidences of regression of neoplasms from obviously insufficient radiation are apparently contrary to the experimental evidence of their susceptibility, and indicates that influences may exist in the organism which have a restraining effect upon the growth of tumors.

The direct destructive effects of radiation upon neoplastic cells together with the effects produced in the tissue bed by the physiologic processes of the individual constitute what we term "radiosensitivity." Not all neoplasms have the same degree of radiosensitivity, because of the variation of their growth characteristics which are the result of the differences in the physiologic response of individuals as well as the specific influence of the origin and morphology of the neoplasm. There is no method by which radiosensitivity or the degree of malignancy of a particular growth can always be determined accurately, although systems of classification on the basis of histologic characteristics have been suggested by various workers and some progress is being made. Unfortunately, these methods must vary considerably according to personal judgment, not only as to the morphology of the neoplastic cells, their origin and their arrangement, but also as to the comparative degree of reaction in the tissue bed, the manifestations of which are the cellular infiltration and fibrosis. We have learned by experience rather than by experimental evidence that most carcinomas are quite resistant to radiation, and their elimination requires ten to fifteen times as great intensity as is necessary to cause a skin reaction. Since it is impossible to predetermine the radiosensitivity of any particular growth, it is still necessary in every case of carcinoma to administer the maximum dose that eliminates the average resistant growth and one that does not interfere with the normal physiologic response of the patient.

From the standpoint of the physics of radium, the rate of absorption in tissues of the average dose of radium which is administered to a carcinoma of the uterine cervix leaves only 13 per cent of the applied intensity at a distance of 5 centimeters. Thus if 10 erythema doses are given at the cervix, only one-half an erythema will reach outside the uterus. Therefore, although this dose of radiation may eliminate most carcinomas which are confined to the uterus, it will not be sufficient to eliminate disease in the parametria or deep pelvic lymphatics which are involved in almost every case. Also the absorption of roentgen rays in tissues is so great that little more than 40 per cent of the skin dose reaches the depth of the uterus, and even under the best of conditions, the total dose which can be administered into the pelvic cavity by cross-fire technic is seldom more than 110 per cent of the skin dose. Hence it may be seen on both a physical and a biological basis that

neither radium nor roentgen rays alone can be depended upon to eliminate malignant disease of the uterine cervix when the parametria or deep pelvic tissues are involved. Fortunately, radium and roentgen treatment may be combined so that the maximum of radiation intensity required may be applied rapidly or over a longer period according to the technic which is indicated or preferred. It is also obvious that, on the basis of knowledge of the physical effects of radiation and of the known biologic effects, a patient with carcinoma of the cervix who has been treated either by radium or roentgen rays alone and who has not had the combination of roentgen rays and radium has not had sufficient irradiation.

Before the development of the high voltage roentgen apparatus, our patients with carcinoma of the cervix were treated by radium alone. While the results were fairly satisfactory and encouraging in early cases, they were not much better than those obtained by surgical procedures. About ten years ago, the method was changed to a combination of radium and roentgen irradiation. A very intensive course of roentgen rays was administered immediately following the application of radium and in the shortest possible time. This procedure soon was abandoned because so many patients had the primary reactions of uncontrollable nausea and malaise followed by secondary reactions of anemia, cystitis, and proctitis, and it was believed that the clinical results did not warrant such drastic treatment. The next step was toward moderation and the technic now employed is to apply radium, using not less than 250 millicuries for approximately 3000 milligram hours, and three to four weeks later a course of roentgenotherapy is begun. I do not apply the roentgen rays to the cervix with the idea of administering a large dose in a short time, but of irradiating the pelvic cavity homogeneously and comparatively slowly with moderate daily doses in order to increase the fibrous tissue reaction in the parametria and in the deep pelvic lymphatics which are beyond the sphere of radium activity.

Not infrequently, patients are encountered in whom the disease has advanced so far that the possibility of applying radium is precluded. In this type of case, it is advisable to begin the roentgenotherapy first, and if the growth regresses, thus indicating its radiosensitivity, treatment with radium is administered which is followed later by another course of roentgenotherapy.

In those patients presenting clinical evidence of deep pelvic metastases and hopelessly advanced malignancy, and in those in whom previous treatment obviously has been inadequate, roentgen irradiation alone is employed as a palliative measure. In such instances the growth is retarded to some extent and pain usually is greatly relieved, especially if the treatment is given in moderate daily dosage over a period of two

to three weeks. The results in most of these cases are discouraging as far as the possibility of cure is concerned but, nevertheless, the treatment is worth while from an economic standpoint because many of these patients are thus enabled to go about their duties for some time before finally becoming bedfast.

Since the combined radium and roentgen technic in the treatment of primary carcinoma of the uterine cervix was adopted, the results secured have been more satisfactory, as indicated by the fact that from 10 to 20 per cent more patients are relieved than by the other procedures. A review of our series of 303 cases of primary carcinoma of the cervix, representing all degrees of involvement, treated between 1920 and 1931 inclusive, shows that 25 per cent of the patients are alive and free from evidence of disease for five or more years, and that 29 per cent of the group treated from three to five years ago also are entirely well.

It may be concluded that our efforts in treating malignant diseases by irradiation should be directed not only to employing radiation for its direct destructive effect upon tissues but also to encourage the physiologic processes which are established to restrain the growth of neoplasms. If radium alone is depended upon to treat carcinoma of the cervix, some patients with disease outside its range of activity will not be cured. Roentgenotherapy in the treatment of carcinoma of the uterine cervix should be employed as an adjuvant to treatment with radium in order to increase the quantity of radiation; it is also useful as a palliative measure in advanced cases. Patients with carcinoma of the cervix who have not had the benefit of combined treatment with radium and roentgen rays have been inadequately treated according to our present knowledge.

THE FRIEDMAN TEST
TECHNIQUE AND INTERPRETATION

W. KENNETH CUYLER, M. A.

The Friedman test[1] was devised principally to aid in the early diagnosis of pregnancy. The test can also be used for diagnostic purposes in a number of other conditions in which there may be reason to suspect an excess of gonadotropic hormone in the urine.[2] This is especially true in conditions of pituitary dysfunction due to a primary pituitary hyperactivity or secondary pituitary hyperactivity resulting from hypogonadism including the menopause and where there is chorionic epithelium in the body. In cases of pituitary tumor the test is useful not only in estimating the degree of hyperactivity of the gland, but also in checking the decrease in pituitary activity once roentgenotherapy has been started. The use of Friedman tests at frequent intervals when patients are being treated with roentgenotherapy for pituitary tumor often indicates a reactivation of the glandular tumor after a period of quiescence. The degree of the positive reaction, found so often at the onset of the menopause, may be of considerable value in governing ovarian therapy in order to relieve the symptoms due to the secondary pituitary hyperactivity.

Although the test is primarily qualitative, with care it can be used in a roughly quantitative manner. In order to accomplish this, certain features of the reaction which are herein described require special attention.

The Friedman test is done at the Cleveland Clinic according to directions received in a personal communication from Dr. Maurice Friedman in 1931. Slight modifications having to do with the collection of the urine and not with the actual technique of the test were instituted by Dr. E. Perry McCullagh.

TECHNIQUE

The urine: One of the modifications made by Dr. McCullagh was the collection of a concentrated morning specimen of urine for the test instead of using a routine specimen. The fluid intake is restricted to six ounces from 4 p. m. on the day preceding the collection of the specimen until it is collected the following morning. All urine voided during the evening and night is discarded and only the first morning specimen is saved for the assay. Except in cases where there is a disturbance in the water metabolism, the specific gravity of a morning specimen under these circumstances should be above 1.020.

The urine is refrigerated for some hours before it is injected; this causes a precipitation of phosphates and urates which are filtered out. Cloudy urine is never injected. If the urine be alkaline, it is acidified

with hydrochloric acid until it is acid to litmus paper. The urine is warmed to approximately body temperature before it is injected.

The animals: With the exception of the chinchillas, all varieties of rabbits used have been used quite satisfactorily.

It has been found that rabbits that have had young are preferable to virgins. In virgin rabbits quite a large percentage have ovaries which are inactive and apparently remain so throughout life. Such animals, of course, cannot be used. If an animal has had young, one would infer that the ovaries function normally. If the rabbit is tested with pregnancy urine before she is used as a test animal and if a reaction is noted, one is doubly confident of the reliability of readings of future tests. We have tested virgin rabbits with pregnancy urine over a period of years, using the technique described above and some never give a positive reaction while others give a positive reaction on one specimen but not on another.

Method: Using a nonpregnant adult female rabbit, 4 cc. of acid urine are injected intravenously three times daily for two days. The marginal ear vein and a 23 gauge needle are used. Forty-eight hours after the first injection the animal is opened under ether anesthesia and the ovaries examined.

In using this test, the following points must be kept in mind:

1. Alkaline urine is never injected.

2. If unusually large quantities of acid are required to neutralize the urine, it is frequently found to be so toxic that it kills the test animal. Under these circumstances, it is therefore usually best to obtain another specimen. However, the test can occasionally be successfully completed by making two injections an hour and a half apart, using 2 cc. at each injection.

3. The urine must always be refrigerated and filtered and if it is cloudy after filtration, it should not be used since it usually results in the death of test animals.

4. The urine should be injected slowly; two cc. per minute.

5. Handle the rabbits gently in order to prevent injuries to the lumbar nerves thus causing paralysis of the posterior portion of the body.

6. Specimens of urine from women who are being treated for pelvic inflammatory disease usually kill rabbits on the first injection.

7. Test rabbits should be kept in strict isolation, contrary to the opinion of some workers. False coitus or even mechanical stimulation of the vulva will produce ovulation and hence ruptured follicles and corpora lutea.

8. The rabbits can be used reliably for another test ten days after a positive reaction has been obtained even though ruptured or hem-

orrhagic follicles, or fresh corpora lutea were present at the last test. The ruptured follicles will have disappeared in that time. Hemorrhagic follicles do not disappear, but recede to a small and firm black spot that is *not raised above the surface of the ovary.* If there is any doubt about the freshness of a hemorrhagic follicle, it should be pierced with a needle; a fresh one will ooze blood, while in an old one the blood has coagulated.

Fresh corpora lutea may easily be distinguished from atretic corpora lutea by the network of fine capillaries which cover the surface, the nodular appearance, and the distinct elevation above the surface. The color is also a distinguishing characteristic. Fresh corpora lutea in the rabbit are not yellow as the name implies, but are pinkish yellow. Old corpora lutea are chalk-white; they have lost the surface capillaries and are not distinctly elevated above the surface of the ovary.

9. Immediately upon opening the rabbit it is advisable to note the amount of congestion of the uterine horns. Handling causes rapid congestion of the organs.

Interpretation

An excess of gonad-stimulating hormone, if it be great enough, produces a positive Friedman reaction. By a positive Friedman reaction is meant the production of either ruptured or hemorrhagic follicles, or fresh corpora lutea. The reaction that may occur in other parts of the reproductive tract is not taken into consideration. An excess may be excreted in a number of conditions other than pregnancy and in both male and female.

For five years an arbitrary method has been used in this institution for recording the results of Friedman tests. It was found that all the significant changes in the genital tract of a female rabbit could be recorded in a tabular manner. The degree of reaction is noted in plus signs, one to four signs being used. A typical positive reaction is indicated in the following table. The degree of reaction can be compared with the normal activity of the organs which also is indicated.

		Normal			*Normal*
Swelling of Uterus	+++	0 to +	Mature Follicles	+	0 to ++
Congestion of Uterus	++++	0 to +	Ruptured Follicles		0
Congestion of Oviducts		00 to +	Hemorrhagic Follicles	+++	0
Congestion of Ovaries		0	Fresh Corpora Lutea		0

Discussion

As mentioned previously, there are different types of positive reactions; likewise there are different types of negative reactions.

According to the table above, one can see that a marked reaction may occur in the uterine horns, oviducts, and ovaries without any marked follicular activity in the ovaries. An abnormal amount of swelling of the uterine horns and an abnormal amount of venous congestion in the uterine horns, the oviduct, and the ovaries, although they do not constitute a positive Friedman reaction, are considered to be due to an excess of sex-stimulating hormone in the urine. The normal size and degree of congestion of the uterine horns and ovaries of the rabbit must be determined by experience.

The type of congestion and swelling of the uterine horns in positive Friedman reactions can be correlated with the reaction in the ovaries in most cases in aiding in accounting for the excess.

The injection of urine from pregnant women will produce a type of congestion in the uterine horns of the animal that is not simulated in a positive reaction caused by other conditions. The amount of swelling and congestion gives the uterus a velvety, transparent appearance, even though the color of the horns may be a purplish-black. This is accompanied by distinct convolutions of the uterine horns into a series of closely associated u-shaped figures. It is the opinion of the writer that in pregnancy the reaction in the ovaries varies in accordance with the duration of the pregnancy. During the first trimester, positive tests may be entirely different. Pregnancies of four weeks or less, *as a rule*, produce positive reactions indicated only by ruptured follicles. Pregnancies of five and six weeks usually produce both ruptured and hemorrhagic follicles. After six weeks of pregnancy and up to the seventh month, positive reactions, *as a rule*, are characterized only by hemorrhagic follicles. After the seventh month ruptured follicles and fresh corpora lutea predominate over hemorrhagic follicles. In most positive reactions in very early and late pregnancy, no hemorrhagic follicles are found. There are, of course, exceptions but they are few.

Positive Friedman reactions have been found during the menopause, in the presence of pituitary basophilism, hypogonadism in both males and females, diabetes mellitus, pituitary tumor, myopia, keratoconus, migraine, hyperthyroidism, prostatic hypertrophy, and testicular tumor, in some conditions of hyperpituitarism such as acromegaly, in some instances of hypertension, and in the presence of tumors containing chorionic epithelium. A positive reaction due to any of these conditions can usually be distinguished from that due to pregnancy by the characteristic appearance of the uterine horns rather than by the reaction in the ovaries. The uterine horns may be swollen and greatly congested

but they do not have the velvety appearance nor are they convoluted as is characteristic of the uterine horns in the positive reaction of pregnancy.

Summary

1. A review of the technique for the Friedman test has been made and attention called to various points in the technique which might prove difficult for the beginner.

2. The nature of the reaction in the oviducts and the uterine horns as well as that in the ovaries is discussed. It is shown that, by using these observations, the scope of the Friedman test can be considerably enlarged.

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EXOPHTHALMOS*

A. D. Ruedemann, M. D.

Bilateral Exophthalmos

Malignant exophthalmos: Malignant exophthalmos and unusual instances of toxic goiter present some of the most serious problems with which the ophthalmologist has to deal in treating diseases of the glandular system. This group of patients requires special consideration and attention, first, because in the true cases, no exophthalmos existed before operation and secondly, because a review of the histories of these patients reveals certain features which make one realize that structures other than the thyroid gland must be involved, although the clinical picture is largely that of hyperthyroidism. The pulse rate may not be extremely high and the loss in weight may not be great. The basal metabolic rate is inconsistent and usually is not so high as would be expected in cases in which a great deal of weight has been lost.

True malignant exophthalmos appears after operation. The patient notices that the eyes are beginning to protrude and this progresses if no treatment is received. When the patients are seen early, the use of thyroid extract up to the point of tolerance often checks the progress of the ocular changes. Large quantities of glandular extract are tolerated well, but the medication must be controlled by repeated estimations of the basal metabolic rate. The edema is that of a severe myxedema, both in the upper and lower lids, and the patients may gain weight. Unless care is exercised, these patients may be thought to have recurrent hyperthyroidism, and a second thyroidectomy may be performed which may result in serious impairment of the general health and may lead to anterior luxation or even to death.

Patients with this disease have terrific venous engorgement; they may have papilledema, and they are extremely uncomfortable because of headaches. One of our patients had associated increased intracranial pressure which persisted for a long time after operation.

"Decapping" of the orbit (Naffziger) is the best approach for the emergency relief of this condition because it corrects the acute condition whereas general treatment can only improve or check it. Deep roentgenotherapy is now being used in the treatment of four patients, and in none of them is the exophthalmos progressing as before.

Further study, adequate treatment, and better selection of cases before operations are performed on the thyroid gland, will reduce the incidence of this condition. However, a number of our patients in whom

* This is the third of four papers on exophthalmos and protrusion of the eyeball. The final paper will appear in the April issue of the Quarterly.

this complication developed were studied preoperatively as thoroughly as possible in the light of existing knowledge of thyroid disease. This distressing condition probably results because certain phases of thyroid disease and interglandular relationships are not understood.

Hypometabolism: Many patients with hypometabolism suffer from severe ocular disturbances which are not relieved by glasses and hence these individuals go from oculist to oculist seeking relief that can only be supplied by treatment of the general disease. The majority of the patients in this group are between forty and sixty years of age and they usually present themselves because of headaches and fatigue.

The headache is suboccipital in character, but of ocular origin and is due to a weakness of the accommodation-convergence (Moebius' sign). In an attempt to offset the weakness of the eye muscles the patient uses the neck muscles so that pain develops at the site of insertion of the muscles along the superior and inferior nuchal lines on the skull and the sternocleidomastoides at the tip of the mastoid. The pain in the head appears at about 10 o'clock in the morning, from 3 to 4 o'clock in the afternoon, and again after dinner at night. It is usually worse at the end of the week or after an evening of bridge, and it may be worse in midwinter, because of reading with a poor light. The convergence-divergence ratio may drop down as low as 1 to 1, although 3 to 0 is the usual ratio. The rapid muscular fatigue is apparent in other muscles of the body as well, and these patients suffer from chronic general fatigue.

Externally, the outstanding feature in cases of hypothyroidism is edema of the upper and lower lids which is similar to that seen in longstanding cases of toxic goiter, in postoperative exophthalmos, and in some cases of hypertension. The edema is worse in the morning but usually persists throughout the day, and it cannot be reduced by massage or pressure.

The exophthalmos, which may not have been noticed by the patient, may range as high as 25 mm. anteroposteriorly. This type of exophthalmos may be attributed to marked gain in weight and is the result of pseudo or true myxedema. (I have not had an opportunity to examine the tissue in any of these cases, so do not know the histologic picture it presents.) The protrusion is usually bilateral and equal. In my series of cases, the difference between the measurements in the two eyes was not greater than 2 mm. and no instance of unilateral exophthalmos was observed. The protrusion does not retract with treatment and continues to increase slowly unless thyroid extract is administered daily. Usually only small amounts are necessary to keep the metabolic rate at a normal level.

The fissures are normal, rarely being wider than 10 to 11 mm. Certainly they present no diagnostic signs although, with the eye well forward, lateral inspection may reveal a larger stretch of sclera to the external angle. Ptosis and other lid signs are absent, as are muscle palsies. Itching of the lids, smarting and burning with mild photophobia may be present.

Gain in weight and a low metabolic rate, slow pulse, low blood pressure, lassitude, lack of ability to concentrate, and inability to work a whole day comprise the symptoms of hypothyroidism. General improvement may not be associated with local improvement in the eyes, and muscle exercises often are of little avail. Prisms which are used in close work are a necessity for accountants and persons who are using their eyes for close, confining work.

Hypertension: A number of our cases of malignant exophthalmos were associated with malignant hypertension, and in these instances, the protrusion was extreme, severe, and uncontrolled by ordinary therapeutic measures. Hypertension *per se* is not usually associated with exophthalmos, but in some instances in which the high blood pressure is of long standing, mainly in malignant hypertension, proptosis is evident. The exophthalmos is bilateral, is not severe, and is associated with edema of the upper and lower lids which is similar to that in patients with hypometabolism.

Associated with the high blood pressure and exophthalmos are vascular changes, rapid pulse, edema of the discs, and a capillary loss in the conjunctival vessels. The patients have headaches on arising in the morning, but these may disappear during the day. Dizziness, nausea, and other symptoms are also present.

The infrequent association of exophthalmos and hypertension makes me feel that the patients in whom both diseases develop will eventually be considered to have a special type of vascular disease. The patients I have observed were never aware of the exophthalmos nor were there any associated signs, such as widening of the fissures or changes in the lids, aside from the persistent edema. No diagnostic value can be attached to the sign of protrusion although it may be 6 to 8 mm. more than a high normal. The exophthalmos persists, although it may vary from 2 to 3 mm. from day to day, but it is slowly progressive. In the patients we have seen, the exophthalmos was not benefited by any treatment prescribed. All the patients died before they experienced any serious difficulty with their eyes.

Ocular Allergy: In my experience ocular allergy has produced only one case of exophthalmos. The edema was bilateral and transitory. The patient had a high eosinophil count and a definite history and

positive reactions to certain allergens. Treatment for the allergic state relieved the ocular edema.

If a patient complains of a sensation of congestion with some local irritation, follicular conjunctivitis, or smarting and burning, the possibility of an allergic basis should be borne in mind and adequate skin tests should be carried out to prove or disprove the diagnosis.

Venous and arteriovenous angioma: Venous and arteriovenous angiomas of the brain are rare conditions. Harvey Cushing and Percival Bailey, L. Brock and Cornelius Dyke have discussed this subject and have noted the occurrence of exophthalmos in several cases. The cerebral involvement is not apparent unless roentgen studies, careful examination of the retina, and studies of the visual fields are made. Furthermore, the reflex pathways must be mapped out to elicit localizing signs of vascular involvement. In studying one of these cases of arteriovenous angioma after operation, I was surprised to find a similar modified arrangement in the conjunctival vessels. Other cases of telangiectasia have frequently revealed minute capillary varices or capillary loops of the simplest form of vascular whirls in the conjunctiva. Undoubtedly, disturbance of the vascular system occurs with sufficient frequency to warrant attention.

Ring, in an excellent case report, studied a severe venous aneurysmal disturbance before and after operation, and published the complete findings. Our experience is quite similar to his. The diagnosis is very difficult, and although the process may be localized by means of encephalography and neurologic study, the actual diagnosis is made at the time of the operation.

Brain tumors may produce proptosis by pressure on the venous outflow, which in turn produces orbital edema. This is usually bilateral, although in one well-remembered instance, unilateral edema of the disc and exophthalmos were produced. Bilateral orbital invasion by brain tumors is not unusual, and several such instances have been reported.

Orbital varices, as such, are not encountered frequently enough to warrant more than mention. I have seen two cases which were unilateral and were easily diagnosed.

Study of the eyes, retinae, visual fields, and conjunctival capillaries are indicated in cases of questionable protrusion, for my experience has been that, even with most questions as to localization answered, there is still enough confusion to warrant complete study in each instance.

Decrease in the Size of the Orbit

Any decrease in the size of the orbital cavity results in exophthalmos. The orbital vaults are not often disturbed by bilateral new growths, and increased intracranial pressure never changes the shape of the orbits after calcification has taken place. The shape of the orbit is a protection

against this and unless some bony new growth develops, the orbits are not involved bilaterally.

Osteitis deformans (Paget's disease): Patients with Paget's disease are not seen by ophthalmologists often enough for them to present an important diagnostic problem; however, this condition does produce exophthalmos in rare instances. In a series of eleven cases seen at the Cleveland Clinic, protrusion of the eye was present in only one instance, and this resulted from orbital bony invasion, rather than from change in the shape of the orbit.

A more common eye complication in this disease is involvement of the optic nerve because of encroachment on the optic canal. Changes in the skull are clearly shown roentgenographically, and bowing of the legs with changes throughout the bony framework are sufficient to permit diagnosis of the condition. Although diagnosis is easy, treatment in valueless. These patients usually live out their full expectation, but may become blind before death supervenes.

Leontiasis ossea: A condition comparable with osteitis deformans is leontiasis ossea (Lion face). I have not seen any of these patients, but one case has been reported in which exophthalmos was bilateral. Roentgen examination is necessary for differential diagnosis in diseases affecting the bones of the face, especially of the forehead.

Acromegaly: In a review of our cases of acromegaly, exophthalmos was not found in any instance. Ivan Lillie, in reviewing a series of cases, found one instance of exophthalmos. Optic atrophy and other eye signs are more frequent and relative enophthalmos, due to enlarged frontal fossae, is quite frequently seen. In spite of its rarity, acromegaly is a possible cause of exophthalmos, and one case has been reported in which this condition resulted in anterior luxation. The diagnosis is not difficult and roentgenography is a valuable aid. Treatment by removal of the tumor of the pituitary or deep roentgenotherapy may be of considerable benefit to the patient.

Relaxation of the orbital fascia: A slight degree of exophthalmos may be produced by relaxation of the orbital fascia and muscle paralysis. The diagnoses in two cases of this type which accompanied thyroid disease were missed at first observation because the picture was obscured by the mental state of the patient in one case, and because of incomplete study in the second.

Summary

All cases of bilateral exophthalmos deserve thorough study because the condition offers valuable information as a sign of systemic disease. Exophthalmos of slight degree warrants careful investigation, for its recognition may lead to the diagnosis of an insidious general condition, especially some type of hypometabolism. The main value of such

study is early diagnosis, for when the protrusion is well advanced, recession is slight or negligible in most instances. This is because the early changes of venous stasis and edema are rapidly replaced by lymphocytic infiltration and fibrosis as the exophthalmos progresses. Each individual case presents a different problem. Although much of the treatment is of little value, some patients are aided tremendously by various measures.

An important problem in exophthalmos is the disturbance of muscle balance and difficulty in use of the eyes for any type of work. Rapid fatigue, pain, photophobia, labyrinthitis, and frequent changes of glasses are all secondary factors.

Unilateral Exophthalmos

Examination in the presence of unilateral exophthalmos must be thorough and more painstaking than in bilateral exophthalmos because it is much more difficult to make a diagnosis. It is true here, as in bilateral exophthalmos, that the earlier the diagnosis is made, the better the end result.

The history in unilateral exophthalmos is very important, especially in regard to the time of onset, the question of pain, loss of vision, diplopia, elevation of temperature, mental disturbances, and the other symptoms and signs seen in bilateral exophthalmos.

It is well to remember that, although the determination of the degree of exophthalmos is dependent on relative measurements, general statements may be made in regard to the anterioposterior position of the eyes. Fourteen to 20 mm. may be regarded as normal, using a Hertel's exophthalmometer. The difference between measurements of the eyes is usually not sufficient to cause any marked discrepancy and a difference of 2 mm. or less should be disregarded regardless of the instrument or method used. It is in the field of unilateral exophthalmos that measurements are of the utmost importance because they reveal progressive changes which may be compared with a stationary eye. Photographs, inspection, and all other methods of examination are secondary to actual comparative study by measurements.

Unilateral exophthalmos may be due to the following conditions:

I. In Children
   A. Increase in orbital contents
      1. Inflammatory
         a. Panophthalmitis
         b. Orbital cellulitis
         c. Pyocele, pyemic abscess
         d. Cavernous sinus thrombosis; lateral sinus thrombosis
         e. Periostitis, osteitis

f. Tenonitis:
   1. Traumatic
   2. Infectious
   3. Surgical
g. Foreign bodies

2. Non-inflammatory

a. Hemorrhages
b. Intermittent (vascular)
c. Encephalocele
d. Meningocele
e. Dermoid cyst, teratoma
f. Thyroid disease
g. New growths
   1. Sarcoma
   2. Hemangioma
   3. Mucocele
   4. Brain tumor
h. Congenital malformations

II. In Adults

A. Hemorrhage

1. Spontaneous, leukemic
   a. Sclerotic
   b. Hypertensive
2. Asphyxia
3. Scurvy

B. Increase in orbital content

1. Inflammatory

a. Cavernous sinus thrombosis, lateral sinus thrombosis
b. Orbital cellulitis
c. Pyocele
d. Periostitis
e. Tenonitis
   1. Serous
   2. Purulent
f. Panophthalmitis
g. Foreign bodies
h. Granuloma—actinomycosis, mycelium, blastomycosis
i. Hydatid or echinococcus cysts
j. Pseudotumors
k. Tumors

1. Gumma
2. Tuberculoma
3. Carcinoma

2. Non-inflammatory:

a. Air
b. Allergic conditions
c. Osteomata
d. Sarcomata
e. Pulsating exophthalmos (may also be inflammatory)
   1. Trauma (77 per cent)
   2. Spontaneous (23 per cent)
f. Intracranial aneurysm
g. Thyroid disease

C. Decrease in size of orbit

a. Trauma
b. Hyperostosis, exostosis, sclerosing osteitis.
c. Paget's disease
d. Invasion from intracranial growths

Increase in Orbital Contents

Panophthalmitis: The most common cause of panophthalmitis is injury. Perforating wounds from ulcers, pieces of glass, BB shot, dynamite caps and steel are not uncommon agents. The history is very important although many children do not reveal injuries they sustained while doing something that has been forbidden; therefore a plain roentgenogram of the orbit should be taken.

Non-perforating wounds may so traumatize the eye that a secondary inflammatory process is brought on. These may be due to BB shot and wounds from hard blunt instruments, such as falling against sharp corners of tables, etc.

Panophthalmitis may follow a severe debilitating illness, such as undulant fever, meningitis, scarlet fever, typhoid fever, or whooping cough. In this latter group, the patient may be seriously ill and the eye will degenerate with a severe acute course and will not respond to treatment.

The disease must be differentiated from acute conjunctivitis. In the latter there usually is a purulent discharge and the anterior chamber of the eye is not involved. In panophthalmitis there usually is no discharge, but the anterior or posterior chamber will have a purulent exudate. The eye is severely inflamed, there is some protrusion (2-6 mm. unilaterally), considerable pain, possibly edema, an increase in

temperature of one or two degrees, loss of vision, and eventually degeneration of the globe by perforation of the abscess process or resorption, and then phthisis bulbi. There is a remote danger of intracranial extension of panophthalmitis which will result in meningitis and death.

Treatment consists first of complete bed rest. Supportive measures are administered, heat is applied locally, and general therapy consists of some form of fever therapy. In traumatic cases local surgery is necessary to drain a hypopyon ulcer or to cauterize a corneal ulceration.

Orbital Cellulitis may follow panophthalmitis, although inflammation of the orbit may precede degeneration of the globe. Trauma is the most common cause and may be due to injuries by sticks, stones, flying missiles, football, wrestling, boxing, and surgery (enucleation, etc.). The history and roentgen examination are of definite value in establishing the diagnosis.

Cases of non-traumatic cellulitis are those that follow general diseases or a long sickness such as scarlet fever, meningitis, or influenza. This condition may be caused by invasion from the adjacent sinuses. In children up to 7 years of age, the frontal sinuses may be ignored, the antra and anterior ethmoids being the cause of the trouble.

Caries of the petrous bone, extraction of teeth, and periostitis may also be agents in the production of orbital cellulitis. Any acute process around the eye, acute hordeolum, acute dacryocystitis and lid abscess may be factors.

Signs of orbital cellulitis are edema of the lids and conjunctiva, protrusion of the eye, 2 to 10 mm. (usually much greater than in panophthalmitis), and diplopia due to impaired motility. There may be some increase in temperature and increase in the number of white blood cells.

Symptoms are pain on movement of the eye, soreness through the orbit to the side of the head, pain in the head, irritability, some insomnia, lachrymation, photophobia, closure of the lids by pressure edema, and in youngsters when the disease is severe and associated with fever, disorientation may occur.

In association with severe inflammation of the orbit we may have not a meningitis but a meningismus. The number of cells in the spinal fluid is increased but usually there are not as many as in meningitis. The spinal fluid will be free from bacteria and will clear with the diminution of the orbital inflammation.

Treatment consists of complete bed rest, application of heat locally, general supportive measures such as food and liquids, removal of foreign body, and treatment of the sinus infection. In cases of sudden exophthalmos, constant relief of the nasal edema and forced drainage

may save the orbit from incision. Usually there is no pus in the orbit but if there is any question, a long, large-bore needle may be used to find a pus pocket. Great care is necessary in probing or washing the orbit. The incision may be beneficial, but, in those cases in which the orbit is extremely tense due to inflammatory reaction, this is not a measure to be undertaken offhandedly or unnecessarily.

The prognosis usually is good unless a pyocele develops at which time tissue destruction may be great and panophthalmitis may ensue with meningitis, cavernous sinus thrombosis, and death.

There are many slight orbital invasions which are not serious but it is impossible to differentiate these; hence, each should be treated as a serious involvement.

THE FRANK E. BUNTS INSTITUTE

The Frank E. Bunts Institute announces the following course in "Diseases of the Gastro-Intestinal Tract" on Monday, Tuesday, and Wednesday, April 5, 6, and 7, 1937.

DISEASES OF THE GASTRO-INTESTINAL TRACT

Monday, April 5, 1937

8:30 A.M.	Registration.	
9:00 A.M.—9:45 A.M.	Dysphagia: Causes, Differential Diagnosis and Roentgen Findings.	E. N. Collins, M. D.
9:45 A.M.—10:15 A.M.	Esophagoscopy: Treatment of Lesions in the Esophagus.	Paul Moore, M. D.
10:15 A.M.—10:45 A.M.	Surgical Treatment of Diverticula of the Esophagus.	George Crile, M. D.
10:45 A.M.—11:15 A.M.	Dental Pathology as a Factor in Gastro-Intestinal Disease.	C. A. Resch, D. D. S.
11:15 A.M.—12:00 Noon	Diseases of the Stomach and Intestine from a Surgical-Pathological Standpoint.	Allen Graham, M. D.
12:00 Noon—1:00 P.M.	Luncheon.	
1:00 P.M.—2:00 P.M.	Exhibits. Demonstrations.	
2:00 P.M.—2:30 P.M.	Etiology of Peptic Ulcer.	John Tucker, M. D.
2:30 P.M.—3:30 P.M.	Symptomatology, Diagnosis, and Medical Treatment of Diseases of the Stomach and Duodenum.	E. N. Collins, M. D.
3:30 P.M.—4:00 P.M.	Surgical Treatment of Diseases of the Stomach and Duodenum.	R. S. Dinsmore, D. D.
4:00 P.M.—5:00 P.M.	Nutritional Deficiency Disorders in Relation to Diseases of the Gastro-Intestinal Tract.	C. L. Hartsock, M. D.
6:00 P.M.	Dinner.	
8:00 P.M.	Bunts Lecture.	

Tuesday, April 6, 1937

9:00 A.M.— 9:30 A.M.	Gastro-Intestinal Symptoms Due to Cardiovascular Disease.	A. C. Ernstene, M. D.
9:30 A.M.—10:00 A.M.	Luetic Lesions of the Gastro-Intestinal Tract.	E. W. Netherton, M.D.
10:00 A.M.—10:45 A.M.	Differential Diagnosis of Jaundice.	R. H. McDonald, M.D.
10:45 A.M.—11:15 A.M.	Liver Function Tests.	Russell Haden, M. D.
11:15 A.M.—12:00 Noon	Pain in Right Upper Quadrant from the Roentgen Standpoint—Cholecystography.	B. H. Nichols, M. D.
12:00 Noon	Luncheon.	
1:00 P.M.—2:00 P.M.	Demonstrations. Exhibits. Practical Points in the Laboratory.	Alfred Reich, B. S.
2:00 P.M.—2:45 P.M.	Surgical Lesions of the Biliary Tract.	R. S. Dinsmore, M. D.
2:45 P.M.—3:45 P.M.	The Pancreas in Relation to Disease of the Gastro-Intestinal Tract.	E. P. McCullagh, M.D.
3:45 P.M.—4:15 P.M.	Gastro-Intestinal Symptoms Due to Genito-Urinary Lesions.	W. E. Lower, M. D.
4:15 P.M.—5:00 P.M.	The Rôle of the Adrenal Sympathetic Complex in Disease of the Gastro-Intestinal Tract—Exhibit.	George Crile, M. D.
6:00 P.M.	Dinner. Round Table Discussion—Diagnostic Problems.	

Wednesday, April 7, 1937

9:00 A.M.—10:00 A.M.	Regional Enteritis. Ulcerative Lesions of the Colon.	E. N. Collins, M. D.
10:00 A.M.—10:30 A.M.	Management of the Patient with Pyloric and Intestinal Obstruction from Chemical Standpoint.	Russell Haden, M. D.
10:30 A.M.—11:15 A.M.	The Acute Abdomen.	R. S. Dinsmore, M. D.
11:15 A.M.—12:00 Noon	Allergy as a Factor in Gastro-Intestinal Disease.	I. M. Hinnant, M. D.
12:00 Noon	Luncheon.	
1:00 P.M.—2:00 P.M.	Exhibits.	
2:00 P.M.—2:30 P.M.	The Use of the Proctoscope in the Diagnosis of Disease of the Anus and Rectum.	T. E. Jones, M. D.
2:30 P.M.—3:00 P.M.	The Roentgen Examination of the Colon (Double Contrast Method).	J. C. Root, M. D.
3:00 P.M.—4:00 P.M.	Surgical Diseases of the Colon and Rectum.	T. E. Jones, M. D.
4:00 P.M.—5:00 P.M.	The Management of Surgical Complications.	George Crile, M. D.

Thursday, April 8, 1937

Surgical Clinics.

REGISTRATION BLANK

_____, 1936

The Frank E. Bunts Institute
Cleveland Clinic
Cleveland, Ohio

Gentlemen:

Please register me for the course in "Diseases of the Gastro-Intestinal Tract," which is to be given April 5, 6, and 7, 1937.

I am enclosing a check for $5.00 and the remainder of the fee, $5.00, will be paid on registration, April 5.

Name_____

Address_____

_____

Medical School from which graduated.

NOTE: Checks should be made payable to The Frank E. Bunts Institute and sent to A. D. Ruedemann, M.D., Cleveland Clinic, Cleveland, Ohio.

Exhibits

Roentgen Findings in Diseases of the Gastro-Intestinal Tract ..... Dr. E. N. Collins

Nutritional Deficiency Disease ..... Dr. R. L. Haden

Dietary Treatment of Urinary Calculi ..... Dr. C. C. Higgins

Manifestations of Allergy in the Gastro-Intestinal Tract ..... Dr. I. M. Hinnant

Carcinoma of the Rectum and Colon ..... Dr. T. E. Jones

Charts Demonstrating the Biochemistry and Physiology of Digestion ..... Dr. D. Roy McCullagh

Protamine-Zinc-Insulin in Diabetes ..... Dr. E. Perry McCullagh

Use of Pitressin as an Aid in Cholecystography ..... Dr. J. C. Root and Dr. E. N. Collins

Wax Models of Lesions of the Gastro-Intestinal Tract.

The Museum of Comparative Anatomy of the Energy-Controlling Mechanism will be open.

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Suggestions for special demonstrations or lectures on specific subjects will be appreciated.

Please send any suggestions you may have to A. D. Ruedemann, M. D., and every effort will be made to include them in this course.